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<p>(54) Title: ANTI-ANGIOGENIC GENE THERAPY VECTORS AND THEIR USE IN TREATING ANGIOGENESIS-RELATED DISEASES</p> <p>(57) Abstract</p> <p>A method for inhibiting tumor growth in a human patient harboring a solid tumor, said method comprising administering to said patient a nucleic acid molecule which expresses in said patient an anti-angiogenic polypeptide selected from the group consisting of human angiostatin, murine angiostatin, human endostatin, murine endostatin, and angiogenesis-inhibiting fragments thereof, wherein expression of the anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells, thereby inhibiting its growth.</p>			

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ANTI-ANGIOGENIC GENE THERAPY VECTORS AND
THEIR USE IN TREATING ANGIOGENESIS-RELATED DISEASES

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Field of the Invention

This invention relates generally to gene therapy for, e.g., cancer.

Background of the Invention

Angiogenesis is the process by which new capillaries are formed from existing vasculature. It is a complex process which involves proliferation and migration of endothelial cells. It plays a fundamental role in reproduction, development and wound repair. Unregulated angiogenesis, however, can further the progression of many diseases, including tumor growth and metastasis, arthritis, diabetes, and some forms of blindness. For example, there is experimental evidence that limits of tumor size and growth are not the failure of the tumor cells to proliferate, but rather a failure of the tumor to provide sufficient nutrients and waste removal to its constituent cells by recruiting surrounding vasculature.

Summary of the Invention

The invention features a method for inhibiting tumor growth in a human patient harboring a solid tumor, involving administering to the patient a nucleic acid molecule which expresses in the patient an anti-angiogenic polypeptide selected from the group consisting of human angiostatin, murine angiostatin, human endostatin, murine endostatin, and angiogenesis-inhibiting fragments thereof, wherein expression of the anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells, thereby inhibiting its growth.

In a second, related aspect, the invention features tumor inhibition, of

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the type just described, using nucleic acids molecules of the formula A-B, where A and B are polypeptide and/or export signal joined by a peptide bond; peptide A contains at least 100 amino acids and includes at least kringle 1, 2, and 3 of human or murine angiostatin; and peptide B contains at least 100
5 amino acids and includes at least 75% of the amino acid sequence of human or murine endostatin. Expression of the fusion anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells, thereby inhibiting its growth. In some embodiments
10 of this hybrid polypeptide and/or export signal method, polypeptide and/or export signal A further includes kringle region 4 of angiostatin, and can also include kringle region 5 of plasminogen (the larger protein molecule of which angiostatin is a portion).

In both aspects of the invention, the nucleic acid molecule preferably
15 constitutes a portion of a viral vector or a plasmid, which can either be administered to the patient so that cells of the patient in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells are infected or transfected with the nucleic acid encoding the angiogenesis-inhibiting
20 polypeptide, or cells (of the patient, or another human donor, or an animal) are infected or transfected *ex-vivo*, and those infected or transfected cells are then infused into the patient so that the anti-angiogenic polypeptide is expressed in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells.

25 As will be discussed in more detail below, in particularly effective embodiments, the nucleic acid molecule includes a nucleotide sequence

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encoding a preactivation polypeptide and/or export signal for effecting Golgi and/or endoplasmic reticulum export of the anti-angiogenic polypeptide.

In another aspect, the invention features a method for treating a human patient suffering from diabetic retinopathy, involving administering to 5 the patient one of the nucleic acid molecules described above.

The above and other features, objects and advantages of the present invention will be better understood by a reading of the following specification in conjunction with the drawings.

Brief Description of the Drawings

10 Fig. 1 depicts the structural relationship of angiostatin with plasminogen.

Fig. 2 depicts the structural relationship of endostatin with collagen type XVIII.

15 Fig. 3 depicts various viral (A. MSCV murine retrovirus; B. Adeno-associated virus; C. HIV based retrovirus; E. recombinant adeno-virus) and non-viral (D. plasmid) vectors used in the construction of gene therapy vectors for this invention.

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MSCV:	Murine Stem Cell Virus
LTR:	Long Terminal Repeat
RSV:	Rous Sarcoma Virus
ITR:	Inverted Terminal Repeat
HIV:	Human Immunodeficiency Virus
IRES:	Internal Ribosomal Entry Site
GFP:	Green Fluorescence Protein
HBPRE:	Hepatitis B Export Element
RRE:	Rev Response Element
polyA:	polyadenylation site
$\psi+$:	viral packaging sequence

The inverted triangle shows the site at which the anti-angiogenic constructs will be inserted using engineered *Mlu*I and *Xho*I restriction sites.

* denotes specific mutations within the long terminal repeat and leader which bestows the ability for expression in embryonic stem and hematopoietic stem cells.

The arrow denotes the direction of transcription.

Fig. 4 depicts in the left (A) panel nude mice which were implanted with human neuroblastoma cells (line SK-N-AS) transduced with a mock virus and in the right (B) panel, nude mice which were transplanted with human neuroblastoma cells transduced with a retroviral gene therapy vector encoding an angiostatin-endostatin fusion protein.

Fig. 5 shows the nucleotide sequence (SEQ ID NO: 1) and amino

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acid sequence (SEQ ID NO: 2) of human plasminogen and the nucleotide sequence (SEQ ID NO: 5) and amino acid sequence (SEQ ID NO: 6) of human angiostatin.

Fig. 6 shows the nucleotide sequence (SEQ ID NO: 9) and amino acid sequence (SEQ ID NO: 10) of murine endostatin.

Fig. 7 shows the nucleotide sequence (SEQ ID NO: 3) and amino acid sequence (SEQ ID NO: 4) of murine plasminogen and the nucleotide (SEQ ID NO: 7) and amino acid sequence (SEQ ID NO: 8) of murine angiostatin.

Detailed Description

10 This invention provides gene therapy using a vector having a nucleotide sequence encoding one of the above-identified anti-angiogenic polypeptides. Described below in more detail are some of the components of the vectors and methods of the invention.

By a gene therapy vector is meant a vector useful for gene therapy. 15 Gene therapy vectors carry a gene of interest that is useful for gene therapy. The gene therapy vectors are able to be transferred to the cells of an animal, e.g., a human, and are able to express the gene of interest in such cells so as to effect gene therapy. The vector can be, e.g., chromosomal, non-chromosomal, or synthetic, and can be RNA or DNA. The vector can be, e.g., a plasmid, a 20 virus or a phage. Preferred vectors include, e.g., retroviral vectors, adenoviral vectors, adeno-associated vectors, herpes virus vectors, Simliki Forest Virus-based vector, Human Immunodeficiency virus, Simian Immunodeficiency virus, and non-viral plasmids. A preferred retroviral vector is Murine Stem Cell Virus (MSCV), which is a variant of Moloney Murine Leukemia Virus 25 (MoMLV).

By anti-angiogenic polypeptide is meant a polypeptide which inhibits

angiogenesis. The terms polypeptide, protein and polypeptide and/or export signal are used interchangeably herein. By angiogenesis is meant the process by which new vasculature, in particular, new capillaries, are formed from existing vasculature. Angiogenesis is a complex process entailing numerous 5 steps, including local dissolution of the basement membrane, migration of endothelial cells into the surrounding stroma, proliferation of the endothelial cells at the leading edge to form a migrating column of cells, branching and fusion of the newly formed vascular loops, and formation of a new basement membrane. By inhibiting angiogenesis is meant completely or partially 10 inhibiting the formation of such new vasculature.

In certain embodiments, the anti-angiogenic polypeptide is an anti-angiogenic fragment of plasminogen (in particular, angiostatin), an anti-angiogenic fragment of collagen XVIII (endostatin) or a fusion of the two fragments.

15 Angiostatin is an internal fragment of plasminogen having a molecular weight of 38 or 45 kDa, depending on whether it contains kringle 1-3 or 1-4. In the invention, either can be used, or a molecule including kringle 1-3 and a portion of kringle 4 can be used. Angiostatin can be naturally produced in vivo in small amounts by tumor cells, e.g. murine Lewis lung 20 carcinoma cells, by proteolytic cleavage of plasminogen so as to eliminate the N-terminal portion including the signal polypeptide and/or export signal and the preactivation polypeptide and/or export signal, as well as the C-terminal portion following kringle 3 or 4. Mouse and human angiostatin have been purified and sequenced. In preferred embodiments, the gene therapy vectors of 25 this invention encode angiostatin having kringle 1, 2 and 3, or angiostatin having kringle 1, 2, 3 and 4.

In another preferred embodiment, the anti-angiogenic polypeptide is

endostatin or a biologically active analog or fragment thereof. Endostatin can be naturally produced *in vivo* in small amounts by tumor cells, e.g., murine angiosarcoma cells, by proteolytic cleavage of endogenous collagen XVIII so as to eliminate the N-terminal portion including the signal polypeptide and/or 5 export signal and the preactivation polypeptide and/or export signal, as well as the C-terminal portion following kringle 3 or 4. See Fig.2. Mouse endostatin has been sequenced, and the human molecule (SEQ ID NOs: 17 and 18) forms a portion of collagen 18 (SEQ ID NOs: 19 and 20).

10 The human molecule position and sequence are apparent from an alignment of the active, Lys-terminated active region of human collagen 18 with murine endostatin, such that the C-terminal lysine residues align, bringing the active endostatin sequences into alignment.

15 In yet another preferred embodiment, the anti-angiogenic polypeptide is an in-frame fusion of angiostatin or a biologically active analog or fragment thereof and endostatin or a biologically active analog or fragment thereof. Preferably, the angiostatin or biologically active analog or fragment is 5' of the endostatin or biologically active analog or fragment. In certain embodiments, the angiostatin-endostatin fusion proteins exhibit synergistic anti-angiogenic properties.

20 By fragment is meant some portion of the naturally occurring anti-angiogenic polypeptide. Preferably, the fragment is at least 20 amino acid residues, more preferably at least 50 amino acid residues, and most preferably at least 100 amino acid residues in length. Fragments include chimeric constructs composed of at least a portion of the relevant gene and another 25 molecule. The ability of a candidate fragment to exhibit a biological activity of the anti-angiogenic polypeptide can be assessed by methods known to those skilled in the art, e.g., by its ability to inhibit proliferation of bovine capillary

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cells, or by its ability to inhibit growth of primary tumor cells, e.g., as described herein. See, e.g., Example 9. Also included are fragments containing residues that are not required for biological activity of the fragment or that result from alternative mRNA splicing or alternative protein processing events.

5 Internal or terminal fragments of a polypeptide can be generated by removing one or more nucleotides from one end (for a terminal fragment) or both ends (for an internal fragment) of a nucleic acid which encodes the polypeptide.

10 In preferred embodiments, the gene therapy vector of this invention is capable of hybridizing to the native anti-angiogenesis polypeptide-encoding regions and has at least about 80%, preferably at least about 90%, and more preferably at least about 95%, sequence identity to the native nucleotide sequences, and encodes a polypeptide which has anti-angiogenic activity; or a biologically active fragment of any of the above nucleotide sequences wherein 15 the encoded polypeptide has anti-angiogenic activity.

The nucleotide sequences of the present invention can be in the form of RNA or DNA, and the nucleotide sequence can be double-stranded or single stranded and, if single stranded, can be the coding strand or non-coding (anti-sense) strand.

20 The coding sequence which encodes the anti-angiogenic polypeptide can be identical to the native coding sequences, or can be a different coding sequence which, as a result of the degeneracy of the genetic code, encodes the same anti-angiogenic polypeptide.

25 In certain embodiments, the gene therapy vector also has a nucleotide sequence encoding a signal polypeptide and/or export signal (SP) for effecting secretion of the anti-angiogenic polypeptide. Examples of signal polypeptide and/or export signal include plasminogen signal polypeptide and/or export

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signal. Preferably, the signal polypeptide and/or export signal is 5' (i.e., upstream) of the nucleotide sequence encoding the anti-angiogenic polypeptide.

Preferably, the gene therapy vector has a nucleotide sequence encoding a preactivation polypeptide and/or export signal (PAP), which is a small 5 polypeptide and/or export signal which effects folding and secretion of the anti- angiogenic polypeptide *in vivo*. Examples of preactivation polypeptide and/or export signal include plasminogen preactivation polypeptide and/or export signal, described herein, and PAP's of other proteins in the blood clotting cascade.

10 Preferably, the preactivation polypeptide and/or export signal is positioned 5' of the nucleotide sequence encoding the anti-angiogenic polypeptide. In embodiments which have a signal sequence and an anti- angiogenic polypeptide, preferably the preactivation polypeptide and/or export signal is 5' of the nucleotide sequence encoding the anti-angiogenic 15 polypeptide, and 3' of the nucleotide sequence encoding the signal polypeptide and/or export signal.

We have discovered that results obtained using constructs containing a PAP- encoding nucleic acid sequence are far superior to results using constructs lacking a PAP-encoding sequence. Our hypothesis to explain these 20 unexpectedly superior results with PAP is that, during the complex process by which the anti-angiogenic polypeptide is expressed and processed in living cells, the PAP polypeptide and/or export signal facilitates the export of the polypeptide from the cellular Golgi apparatus and/or the endoplasmic reticulum (ER). The corollary is that, absent PAP, a significant portion of the expressed 25 polypeptide remains trapped in the Golgi and/or ER.

The PAP exemplified herein is derived from human plasminogen; this

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PAP is currently preferred. Our discovery that the use of a PAP dramatically improves results leads us to believe that other PAP's would be useful as well, and such others are therefore contemplated for use in the invention. Thus, as used herein, "PAP" refers to a polypeptide and/or export signal which is naturally associated with a eukaryotic (preferably human) protein, the exportation of which is facilitated by its associated PAP. Examples of other human proteins whose Golgi/ER export is PAP-facilitated include other secreted proteins of the blood coagulation cascade, e.g., fibrinogen, prothrombin, Factor VIII, and Factor IX. Other secreted human proteins also are associated with potentially useful PAPs.

It is not essential that the PAP used in the invention be identical in amino acid sequences to a native PAP; it is well-known that polypeptide and/or export signal that facilitate protein secretion or export, e.g., signal polypeptide and/or export signal and PAPs, can vary from the native forms to a certain extent and still retain their function. Therefore, PAPs useful according to the invention preferably have 75% or greater amino acid sequence identity with a native PAP.

In certain embodiments, the gene therapy vector has a nucleotide sequence encoding a tag for identification of the anti-angiogenic polypeptide and/or export signal. In certain embodiments, the tag is 5' of the nucleotide sequence encoding the anti-angiogenic polypeptide; in other embodiments, the tag is 3' of the nucleotide sequence encoding the anti-angiogenic polypeptide. In embodiments in which the anti-angiogenic polypeptide is endostatin or an angiostatin-endostatin fusion, it is preferred that the tag be 5' of the nucleotide sequence encoding endostatin.

In certain embodiments the gene therapy vector includes a selectable

marker, e.g., a Neomycin phosphotransferase gene, or a humanized red-shifted green fluorescent protein.

The invention also includes a cell infected or transfected with a gene therapy vector described herein. Preferably, the cell is an animal cell, more 5 preferably an autologous or allogeneic human cell. The gene therapy vectors described herein can be introduced into a cell, e.g., by transformation, transfection, transduction, infection, or ex vivo injection. They can be targeted to a particular cell type.

Administration of nucleic acid, e.g., a gene therapy vector, can be 10 accomplished by any method which allows the nucleic acid to reach the target cells. These methods include, e.g., injection, deposition, implantation, suppositories, oral ingestion, inhalation, topical administration, or any other method of administration where access to the target cells by the nucleic acid is achieved. Injections can be, e.g., intravenous, intradermal, subcutaneous, 15 intramuscular or intraperitoneal. Implantation includes inserting implantable drug delivery systems, e.g., microspheres, hydrogels, polymeric reservoirs, cholesterol matrices, polymeric systems, e.g., matrix erosion and/or diffusion systems and non-polymeric systems, e.g., compressed, fused or partially fused pellets. Suppositories include glycerin suppositories. Oral ingestion doses can 20 be enterically coated. Inhalation includes administering the nucleic acid with an aerosol in an inhalator, either alone or attached to a carrier that can be absorbed.

In certain embodiments of the invention, administration can be designed so as to result in sequential exposures to the nucleic acid over some time 25 period, e.g., hours, days, weeks, months or years. This can be accomplished by repeated administrations of the nucleic acid, e.g., by one of the methods described above, or alternatively, by a controlled release delivery system in

which the nucleic acid is delivered to the animal over a prolonged period without repeated administrations. By a controlled release delivery system is meant that total release of the nucleic acid does not occur immediately upon administration, but rather is delayed for some time. Release can occur in bursts 5 or it can occur gradually and continuously. Administration of such a system can be, e.g., by long acting oral dosage forms, bolus injections, transdermal patches or subcutaneous implants. Examples of systems in which release occurs in bursts include, e.g., systems in which the nucleic acid is entrapped in liposomes which are encapsulated in a polymer matrix, the liposomes being 10 sensitive to a specific stimulus, e.g., temperature, pH, light, magnetic field, or a degrading enzyme, and systems in which the nucleic acid agent is encapsulated by an ionically-coated microcapsule with a microcapsule core-degrading enzyme. Examples of systems in which release of the nucleic acid is gradual 15 and continuous include, e.g., erosional systems in which the nucleic acid is contained in a form within a matrix, and diffusional systems in which the nucleic acid permeates at a controlled rate, e.g., through a polymer. Such sustained release systems can be, e.g., in the form of pellets or capsules.

The nucleic acid is administered to the patient in a therapeutically effective amount. By therapeutically effective amount is meant that amount 20 which is capable of at least partially preventing or reversing the disease. A therapeutically effective amount can be determined on an individual basis and will be based, at least in part, on consideration of the patient's size, age, the efficacy of the particular nucleic acid used, the type of delivery system used, the time of administration relative to the onset of disease symptoms, and 25 whether a single, multiple, or controlled release dose regimen is employed. A therapeutically effective amount can be determined by one of ordinary skill in the art employing such factors and using no more than routine experimentation.

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In certain embodiments, a therapeutically effective amount of an anti-angiogenic polypeptide is administered by providing to the animal a nucleic acid encoding the polypeptide and expressing the polypeptide *in vivo*. Nucleic acids encoding the polypeptide, or mutants thereof, can be administered in any 5 biologically effective carrier, e.g. any formulation or composition capable of effectively delivering the nucleotide sequence for the anti-angiogenic polypeptide to cells *in vivo*. Approaches include, e.g., insertion of the nucleic acid into viral vectors. Viral vectors can be delivered to the cells, e.g., by infection or transduction using the virus. Viral vectors can also be delivered to 10 the cells, e.g., by physical means, e.g., by electroporation, lipids, cationic lipids, liposomes, DNA gun, $\text{Ca}_3(\text{PO}_4)_2$ precipitation, or delivery of naked DNA. In certain preferred embodiments, the virus is administered by injection, e.g., intramuscular injection, in a dose range of about 10^3 to about 10^{10} infectious particles per injection, more preferably in a dose range of about 10^5 to about 15 10^8 infectious particles per injection. Single or multiple doses can be administered over a given period of time, depending, e.g., upon the disease.

An alternative is insertion of the nucleic acid encoding the anti-angiogenic polypeptide into a bacterial or eukaryotic plasmid. Plasmid DNA can be delivered to cells with the help of, e.g., cationic liposomes (lipofectinTM; 20 Life Technologies, Inc., Gaithersburg, MD) or derivatized (e.g., antibody conjugated) polylysine conjugates, gramicidin S, artificial viral envelopes or other such intracellular carriers, as well as direct injection of the gene construct or $\text{Ca}_3(\text{PO}_4)_2$ precipitation carried out *in vivo*, or by use of a gene gun. The above-described methods are known to those skilled in the art and can be 25 performed without undue experimentation.

Since transfer of the nucleic acid to appropriate target cells represents the critical first step in gene therapy, choice of the particular gene delivery

system will depend on such factors as the intended target and the route of administration, e.g., locally or systemically. Targets for delivery of the nucleic acid can be, e.g., specific target cells which are diseased. For example, the target can be, e.g., the peritoneal cavity, gastro-intestinal tract, bone marrow 5 cavity, liver, lungs, muscles, vasculature, pericardial cavity, pleural cavity, skin, sub-cutaneous or deep connective tissues, central nervous system, spinal fluid, eye, or specific sites of tumor growth. Administration can be directed to one or more cell types, and to one or more cells within a cell type, so as to be therapeutically effective, by methods known to those skilled in the art. For 10 example, the nucleic acid can be, e.g., coupled to an antibody, to a ligand to a cell surface receptor, or to a toxin component, or can be contained in a particle which is selectively internalized into cells, e.g., liposomes, or a virus where the viral receptor binds specifically to a certain cell type, or a viral particle lacking the viral nucleic acid, or can be administered by local injection.

15 In certain embodiments, the nucleic acid is administered to the patient by introducing *ex vivo* the nucleic acid into cells of the patient, or into syngeneic or allogeneic or xenogeneic cells, and then administering the cells having the nucleic acid to the animal. Any cell type can be used. In certain embodiments, the cells having the introduced nucleic acid are expanded and/or 20 selected after the nucleic acid transfer. The cells having the transferred nucleic acid are subsequently administered to the patient. Preferably, the cells are administered in a dose range of about 1×10^6 to about 1×10^9 cells/dosage/day, and most preferably at about 1×10^7 to about 1×10^8 cells/dosage/day. The cells can be administered by any method which results in delivering the 25 transferred nucleic acid in the cells to the desired target. For example, the cells can be implanted directly into a specific tissue of the patient, or implanted after encapsulation within an artificial polymer matrix. Examples of sites of

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implantation include, e.g., the peritoneal cavity, gastro-intestinal tract, bone marrow cavity, liver, lungs, muscles, vasculature, pericardial cavity, pleural cavity, skin, sub-cutaneous or deep connective tissues, central nervous system, spinal fluid, eye, or specific sites of tumor growth.

5 Systemic delivery can be achieved, e.g., by introducing the nucleic acid into cells which circulate in the peripheral blood of the patient, or which give rise to cells which circulate in the peripheral blood. In certain embodiments, the nucleic acid is introduced into such cells *ex vivo*, and these cells are then administered to the patient, resulting in systemic delivery within the peripheral
10 blood. These cells can be the cells of the patient or allogeneic cells. Preferred cells in which the nucleic acid can be introduced are hematopoietic cells.

In certain embodiments, other therapy is additionally administered. For example, if the animal is being treated for a tumor, other tumor therapy, e.g., another therapeutic agent, chemotherapy, radiation or surgery, is additionally
15 administered to the patient, either simultaneously or at different times.

Treating is meant to include, e.g., preventing, treating, reducing the symptoms of, or curing the disease. I.e. treating a tumor includes preventing growth of the tumor, causing shrinkage of the tumor, or preventing development of micro-metastases.

20 Preferably, the recombinant nucleic acid is a gene therapy vector, e.g., as described herein. Preferably, the anti-angiogenic polypeptide is angiostatin, endostatin, an angiostatin-endostatin fusion protein, or biologically active analogs or fragments thereof. In certain embodiments, the angiostatin has kringle 1, 2 and 3; in other embodiments, the angiostatin has kringle 1, 2, 3
25 and 4, and, in some embodiments, kringle 5 of human or murine plasminogen. Angiostatin is described in O'Reilly and Folkman U.S. Patent No. 5,639,725, hereby incorporated by reference. Endostatin is described in O'Reilly and

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Folkman PCT Appln. No. WO 97/15666, published May 1, 1997, hereby incorporated by reference.

In certain embodiments, the recombinant nucleic acid has been introduced *ex vivo* into cells so as to express the anti-angiogenic polypeptide in the cells, and the recombinant nucleic acid is administered to the patient by administering to the patient the cells containing the recombinant nucleic acid. In certain embodiments, the cells are derived from the patient; in other embodiments the cells are allogeneic cells relative to the cells of the patient.

Where cells are infected or transfected *ex vivo* for later infusion into the patient, the cells are preferably hematopoietic cells, but can also be mesenchymal cells, stem cells, epithelial cells (e.g., from the gut), or dendritic cells.

The gene therapy vectors of the invention can be provided in a pharmaceutical composition comprising a therapeutically effective amount of the recombinant nucleic acid together with a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers include, e.g., water, saline, dextrose, glycerol, ethanol, liposomes and lipid emulsions.

The following non-limiting examples further illustrate the present invention.

20

EXAMPLES

Example 1: Construction of Inserts for Gene Therapy Vectors Containing cDNA for Angiostatin, Endostatin or Angiostatin-Endostatin Fusion Proteins

The following genetic constructs are inserted into retroviral gene therapy vectors; the genetic constructs contain human or murine cDNA for angiostatin, endostatin or an angiostatin-endostatin fusion, and DNA encoding a signal

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polypeptide and/or export signal (SP), a tag (FLAG), and, preferably, a preactivation polypeptide and/or export signal (PAP). The constructs are all made using standard genetic engineering techniques, and their insertion into retroviral gene therapy vectors is carried out using known methods. The 5 constructs have the following components:

Murine Constructs

SP-K1-K2-K3-Flag
SP-K1-K2-K3-K4-Flag
SP-K1-K2-K3-K4-K5-Flag
10 SP-PAP-K1-K2-K3-Flag
SP-PAP-K1-K2-K3-K4-Flag (SEQ ID NO: 11 and 12)
SP-Flag-Endo (SEQ ID NO: 13 and 14)
SP-K1-K2-K3- Flag-Endo
SP-K1-K2-K3-K4- Flag-Endo (SEQ ID NO: 15 and 16)
15 SP-PAP-K1-K2-K3- Flag-Endo

Human Constructs

SP-K1-K2-K3
SP-K1-K2-K3-K4
SP-K1-K2-K3-K4-K5
20 SP-PAP-K1-K2-K3
SP-PAP-K1-K2-K3-K4
SP-PAP-K1-K2-K3-K4-K5
SP-Endo
SP-K1-K2-K3-Endo
25 SP-PAP-K1-K2-K3-Endo

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Nucleic acid and amino acid sequences for mouse and human angiostatin and endostatin used in these constructs are shown in Figs. 5-7.

Nucleic acid and amino acid sequence of the FLAG peptide:

amino terminus-	ASP	TYR	LYS	ASP	ASP	ASP	ASP	LYS
5'-	GAC	TAC	AAG	GAC	GAC	GAT	GAC	AAG

Human plasminogen derivative constructs

The entire coding region of the human plasminogen cDNA from the start (ATG) to the stop (TAA) codon is 2433bp in size.

This sequence encodes a signal peptide (bp 1-57), a preactivation peptide (bp 58-288), and 5 distinct structural regions known as kringle (K1-K3 from bp 289-1092; K4 from bp 1093-1380; K5 from bp 1381-1740). Please note that although I have given precise bp measurements for kringle K4 and K5, it can be argued that the sequence encoding K4 is between bp 1056-1440 and the sequence encoding K5 is between bp 1362-1680.

A DNA fragment encoding a portion of the human plasminogen protein from bp 1 to 1377 was obtained by PCR of a widely available human liver cDNA library using synthetic DNA oligonucleotides complementary to sequences immediately preceding the signal peptide and immediately following kringle 4. This fragment contains the signal peptide (bp 1-57), the preactivation peptide (bp 58-288), kringle 1 (bp 289-549), 2 (bp 550-804), 3 (bp 805-1092) and 4 (bp 1093-1380). The synthetic oligonucleotides used for this reaction contained engineered recognition sites for the restriction enzymes EcoRI and XhoI. Following the PCR reaction the amplified fragment was cloned into the EcoRI/XhoI sites of BluescriptSK(-) (Stratagene) using standard techniques (Maniatis). Following cloning the integrity of the amplified sequence was verified by sequencing both strands using the Sanger method (Sanger). Various derivatives of the cloned fragment were subsequently constructed using BluescriptSK(-) (Stratagene) as a backbone. A full list of the derivatives are described in Table 1. Briefly, the variations are composed of constructs containing various combinations of kringle with or without the signal and/or preactivation peptide sequences. These derivatives were constructed using both standard techniques as well as PCR and the use of double stranded synthetic oligonucleotides. In all cases the integrity of the start codon, coding sequence and termination codon was verified by double stranded sequencing using the Sanger method.

Murine plasminogen derivative constructs

The coding sequence for murine plasminogen is 2439bp in size and, similar to the human plasminogen cDNA encompasses a sequence encoding signal and preactivation peptides (bp 1-57 and 58-288 respectively) in addition to 5 kringle regions; kringle 1-3 (bp 289-1092), kringle 4 (bp 1093-1380) and kringle 5 (bp 1381-1743). Again, although I have given precise bp measurements for kringle K4 and K5, it can be argued that the sequence encoding K4 is between bp 1056-1440 and the sequence encoding K5 is between bp 1362-1680.

The murine plasminogen cDNA has previously been cloned and was made available to us. Derivatives of murine plasminogen were constructed using sequences derived from bp 1-1743 of the coding sequence. Various combinations of kringle regions with or without signal and preactivation peptide regions were made using BluescriptSK(-) (Stratagene, La Jolla, CA) as the vector backbone. These derivatives were constructed using standard cloning techniques (Maniatis, Molecular cloning; a laboratory manual, second edition, 1989) in combination with PCR utilizing synthetic oligonucleotides using

Angiostatin function was not altered by adding the FLAG polypeptide and/or export signal to either the N- or C-terminal ends, whereas endostatin was functional only if FLAG was added to its N-terminal end.

Example 2: Construction of Retroviral Gene Therapy Vectors

5 This example illustrates the construction of retroviral gene therapy vectors comprising cDNA for angiostatin, endostatin or angiostatin-endostatin fusion proteins.

The DNA inserts from Example 1 were inserted into two retroviral vectors. Both vectors were derived from the Murine Stem Cell Virus (MSCV),
10 which is a variant of Moloney Murine Leukemia Virus (MoMLV) having several mutations allowing high, sustained expression in hematopoietic stem cells and their progeny. In both cases, the angiostatin, endostatin, or angiostatin-endostatin fusion DNA inserts were under the transcriptional control of the retroviral left Long Terminal Repeat (LTR). In the first vector,
15 the dominant selectable marker was the Neomycin phosphotransferase gene (NeoR), which confers resistance to G418, and is driven by an internal phosphoglycerate kinase (PGK) promoter. In the second vector, the dominant selectable marker was the humanized, red-shifted green fluorescent protein (EGFP), which is co-translationally expressed by means of an Internal
20 Ribosome Entry Site (IRES) from the Encephalomyocarditis virus (EMCV).

The retroviral gene therapy vectors were transfected by CaPO_4 precipitation in the transient ecotropic packaging cell-line BOSC 23, Pear et al., *PNAS* 90:8392 (1993). Viral supernatants were collected two days thereafter and filtered through 0.45 mm filters. Filtered viral supernatants were
25 subsequently used to infect GENETIX's stable amphotropic retroviral packaging cell-line AM12 (Genetix Pharmaceuticals, Inc., Cambridge, MA). After another two days, viral supernatants from transduced AM12 were filtered

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and used to infect GENETIX's stable ecotropic retroviral packaging cell-line GP+E86 (Genetix Pharmaceuticals, Inc.). Both transduced AM12 and GP+E86 were then selected in the presence of G418 (in the case of constructs bearing NeoR) or sorted by Fluorescent Activated Cell Sorter (FACS) for EGFP expression. Viral titers were estimated according to standard practice by counting G418 resistant colonies among NIH3T3 cells exposed to diluted virus preparation. Ecotropic viral titers were above 5×10^5 /ml of viral supernatants, only 3-fold lower than "empty" control vectors. No Replication Competent Retrovirus (RCR) was detected in standard assays.

10 Example 3: Transduction of Target Cells Using Retroviral Gene Therapy Vectors

This example illustrates the stability of retroviral gene therapy vector transmission and the lack of toxicity in non-endothelial target cells.

Following 24-hour incubation of confluent viral producer cells in 100 mm plates, viral supernatant was removed and filtered (0.45 μ m filter, Gelman Sciences, Ann Arbor, MI). Viral supernatant, containing 7 μ g/ml polybrene (Sigma, St. Louis, MO), was added to target cells 24 hours after plating the target cells. Fresh medium was added after 4-12 hours, and, after an additional 48 hours, cells were selected for retroviral infection by exposure to medium containing 1 mg/ml G418 (Gibco BRL, Grand Island, NY) or by FACS sorting (FACStar cell sorter, Becton Dickinson, San Jose, CA). The stability of transmission of the retroviral gene therapy vectors described in Example 2 was examined by Southern blot analysis of transduced NIH3T3 cells, using specific probes (EGFP) and restriction enzyme digestion of genomic DNA with Sac1, which cuts only once in each LTR. Stable chromosomal integration of intact proviruses of appropriate length was observed with all constructs.

The lack of non-specific toxicity on non-endothelial cells was

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established by using filtered viral supernatants to transduce various tumor cell-types and cell-lines (NIH3T3 cells, K562 cells (ATCC), and human SK-N-AS neuroblastoma cells; Cohen, P.S., *Cancer Research*, 55:2380 (1995).

Transduced cell populations were subsequently selected with G418 or sorted
5 for EGFP expression by FACS. No obvious effects on cell viability, growth or other phenotypical characteristics were detected.

Example 4: Protein Expression of Angiostatin, Endostatin and Angiostatin-Endostatin Fusion Proteins in Cells Transduced with Retroviral Gene Therapy Vectors

10 This example illustrates that recombinant angiostatin, endostatin, and angiostatin-endostatin fusion proteins were readily detected in retrovirally transduced cells and their supernatant, indicating efficient expression and secretion.

MSCV virus based vectors containing sequences encoding murine Kringle 1 (K1), K1K5, K1K2K3, K1K2K3K4, and K1K2K3K4K5 were used to transduce NIH3T3 cells. With regard to the murine recombinant proteins, Western blot analysis of transduced cells and their supernatant was performed by means of a monoclonal antibody that recognizes the FLAG polypeptide and/or export signal. Because this antibody is not mono-specific, significant cross-reactivity with murine proteins was apparent. However, by comparing the pattern obtained with mock cells, it was clear that the antibody revealed an additional band of appropriate size in all transduced cells. Moreover, the recombinant proteins were detected in cell supernatants at levels above 50 ng/ml, using a protein concentration/semi-purification procedure (Centricon 20 columns, Amicon, Beverly, MA). With regard to the human recombinant proteins, no FLAG tag was added, so a monoclonal antibody that recognizes specifically the first three kringle of human plasminogen in its native, non-

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denatured form was used; O'Reilly et al., *Cell* 79:315 (1994). Because of this constraint, Western blot analysis using denaturing gels could not be performed. An ELISA assay was performed which indicated that human recombinant angiostatin was detected at levels likely to be therapeutic according to previous 5 findings in the model of Lewis Lung Carcinoma *Id*.

These results indicate that high levels of recombinant proteins of expected length were expressed in retrovirally transduced cells and were efficiently secreted.

10 Example 5: In Vivo Anti-Tumor Activity of Cells Transduced with Gene Therapy Vectors Encoding the Angiostatin-Endostatin Fusion Protein

Human SK-N-AS neuroblastoma cells (Cohen, 1995) were transduced with the retroviral gene therapy vector containing the angiostatin-endostatin fusion protein, described in Example 2. These cells (1,000,000) were 15 suspended in 1 mL Dulbecco's phosphate buffered saline and injected into the right mid-quadrant of nude immuno-compromised mice. While no impairment of the *in vitro* growth of transduced cells was observed, a dramatic decrease in tumor growth in nude mice cells following subcutaneous implantation of the transduced cells was evident as compared to "mock virus"-transduced control 20 cells.

Example 6: Ex Vivo Transfer of Retroviral Gene Therapy Vectors Encoding Anti-Angiogenic Polypeptides to Primary Hematopoietic Cells, and Subsequent Transplantation to Recipient Mice

This example illustrates infection of primary hematopoietic cells from

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donor mice with retroviral gene therapy vectors encoding angiostatin, endostatin, or an angiostatin-endostatin fusion protein, and a selectable GFP marker, and subsequent transplantation of the transduced hematopoietic cells into recipient mice.

5 Femoral bone marrow cells are harvested from male donor C57BL6/J-Ly5.1 mice (Jackson Labs, Bar Harbor, ME), intravenously injected four days previously with 150 mg/kg of 5-fluorouracil (5-FU). Bone marrow cells are cultured for two days in medium composed of DMEM, 15% fetal calf serum, 10 ng/ml human IL-6, 6 ng/ml murine IL-3 and 100 ng/ml murine Steel factor

10 prior to two days of culture atop a confluent monolayer of irradiated (1,500 cGy, ^{137}Cs γ -irradiation) viral producer cells in the above medium including 6 ug/ml of prolamine sulfate. The viral producer cells are transfected with a retroviral gene therapy vector, as described above. Upon completion of the co-culture infection protocol, recovered non-adherent cells are cultured for an

15 additional 48 hours to allow for expression of the transferred GFP gene.

Retrovirally transduced cells expressing the transferred GFP gene are subsequently identified and selected for, using a FACStar+ cell sorter (Becton Dickinson, San Jose, CA). The GFP+ cells are intravenously injected into congenic female C57BL6/J-Ly5.2 recipient mice (National Cancer Institute, 20 Washington, DC) previously given 950 cGy (83cGy/min, ^{137}Cs γ -rays) of whole body irradiation. In each case, a small fraction of GFP+ sorted cells is used for day 12 CFU-S and in vitro clonogenic progenitor assays to assess the efficiency of the infection and selection procedures on these more mature cell types.

25 Example 7: Engraftment of Recipient Mice with Donor-Derived Hematopoietic Cells

This example illustrates engraftment of the recipient mice with the

donor-derived transfected hematopoietic cells from Example 6.

The donor and recipient mice are phenotypically distinguishable on the basis of Y chromosome specific sequences, as well as on the basis of allelic differences at the murine CD45 cell surface antigen locus. Male donor mice 5 are homozygous for the CD45.2 allele, while female recipient mice are homozygous for CD45.1. The engraftment of recipient mice with donor-derived (CD45.2+) cells is assessed at both short (5 weeks) and long (34 months) time points post-transplant by flow cytometric analysis of peripheral blood samples stained with a phycoerythrin labeled antibody specific for the 10 CD45.2 antigen (Pharmingen, San Diego, CA). The results indicate that engraftment occurs.

Example 8: Proviral Marking and GFP Expression in Recipient Mice

This example illustrates the presence of recombinant provirus and expression of the transferred GFP gene in the recipient mice from Example 6.

15 The level of proviral marking in reconstituted animals is initially determined by Southern blot and semi-quantitative PCR analysis of DNA obtained from peripheral blood leukocytes. The large majority of donor-derived (CD45.2+) cells in recipient mice contain a minimum of one copy of recombinant provirus. In addition, flow cytometric analysis of peripheral blood 20 leukocytes is performed to ascertain the proportion of cells expressing the transferred GFP cDNA. Because the GFP and angiogenic inhibitor protein cDNAs are both driven from the same regulatory sequences, due to the inclusion of an internal ribosomal entry site (IRES) element, the analysis of GFP expression in the peripheral blood provides an indirect measurement of 25 the levels of anti-angiogenic protein being expressed. The results indicate expression of the transferred genes.

Example 9: Anti-Angiogenic Polypeptide Expression in Recipient Mice

This example illustrates the presence of anti-angiogenic polypeptide in the sera of the recipient mice from Example 6, using both physical and functional assays.

5 Serum obtained from the transplanted animals described in Example 6 is used for ELISA using an antibody specific for the synthetic FLAG epitope (IBI, Eastman Kodak, New Haven, CT) and compared against known standards of purified protein. Results indicate the presence of the anti-angiogenic polypeptide in the serum.

10 To determine whether a functional anti-angiogenesis polypeptide is present in the circulation, sera from transplanted animals is tested for its ability to inhibit the proliferation of bovine capillary cells *in vitro*; O'Reilly (1994). Briefly, cells are plated in 24 well dishes at 25,000 cells/ml and maintained in DMEM with 5% bovine calf serum for 24 hours. The medium is then replaced

15 with fresh medium containing various dilutions of the test serum. After 20 minutes of incubation, fresh medium including b-FGF (final concentration 1 ng/ml) is added and the cells are cultured for 72 hours. Cells are then dispersed using trypsin and the cell number determined by Coulter counter. Results indicate that functional anti-angiogenic polypeptide is present in the sera of the

20 recipient mice.

25 In addition, the ability of circulating anti-angiogenic polypeptide to inhibit the growth of primary tumor cells is assessed. Transplanted mice are subcutaneously injected with one million Lewis lung carcinoma (LLC) cells (O'Reilly, (1994)) at the proximal midline of their dorsal skin. The mice are closely monitored for survival, tumor size and growth, and overall health. Results indicate that the anti-angiogenic polypeptides from the sera of the

recipient mice inhibit growth of the LLC tumor cells.

Finally, upon sacrifice of the transplanted recipient mice, blood, spleen, thymus and bone marrow are harvested and analyzed for the presence of proviral DNA by Southern analysis as well as expression of the transferred 5 GFP and anti-angiogenic polypeptide cDNAs by flow cytometry and ELISA. Moreover, a portion of bone marrow cells is re-transplanted into secondary recipients to generate individual day 12 spleen colonies, as well as plated in methylcellulose to assess *in vitro* clonogenic progenitors. Individual clones are analyzed for proviral DNA by PCR or Southern blot, and for gene expression 10 by flow cytometry and ELISA. Results of these tests also indicate the presence of proviral DNA and expression of the anti-angiogenic polypeptides and marker proteins.

15 Example 10: Evaluating the Efficacy of Retroviral Gene Therapy Vectors
Encoding Anti-Angiogenic Polypeptides on Various Human
Cancers Implanted in SCID Mice Using Ex Vivo Gene Therapy

This example illustrates a method for rapidly screening various forms of human cancer to determine susceptibility to treatment by the systemic delivery of anti-angiogenic polypeptides.

The methods for gene transfer, assessment of proviral marking and 20 assessment of transferred gene expression as described in Examples 3 through 9 are repeated using immuno-deficient SCID mice, with the following exceptions. Since SCID mice are more sensitive to γ -irradiation than C57BL6/J mice, the female SCID recipients receive a lower dose of 400cGy of whole body irradiation in contrast to the 950cGy required for C57BL6/J. In 25... addition, since the SCID mice do not possess allelic differences at the CD45 cell surface antigen locus, donor and recipient cells are phenotypically distinguished on the basis of Y chromosome specific sequences using Southern

blot analysis.

Bone marrow from male donor SCID mice is infected, selected for on the basis of expression of the transferred GFP marker cDNA, and transplanted into irradiated female SCID recipients. Engraftment with provirally marked 5 cells and expression of the transferred genes is demonstrated. The mice are then separately implanted with a variety of human tumor cell types, e.g., breast adenocarcinoma, lung squamous cell carcinoma, and brain glioblastoma. In each case, the ability of the anti-angiogenic polypeptides to inhibit the growth of the various human tumor cell types is monitored and quantified.

10 Example 11: Evaluating the Efficacy of Retroviral Gene Therapy Vectors
Encoding Anti-Angiogenic Polypeptides for Treatment of
Ovarian Cancer Using In Vivo Gene Therapy

This example illustrates the feasibility of using retroviral gene therapy vectors encoding anti-angiogenic polypeptides to achieve efficient gene transfer 15 to established tumors in vivo using a well-established murine model of human ovarian cancer. Following injections, mice are closely monitored for tumor growth and survival.

Eight to ten week old nude mice (Jackson Labs, Bar Harbor) are injected intra-peritoneally with 1×10^7 PA-1 cells, an ovarian cancer cell-line (ATCC), 20 and followed until palpable tumors are identified. Viral supernatant for in vivo injection is prepared as follows: Viral producer cells are grown to confluence in DMEM with 10% bovine calf serum, and the medium is then changed. After 24 hours of incubation, the viral conditioned supernatant is filtered through a 0.45 um low protein binding filter, protamine sulfate is added to a final 25 concentration of 6ug/ml, the solution is aliquoted into 2 ml volumes, and frozen at -80°C. Recipient mice receive three intraperitoneal injections of viral supernatant (2 mls per injection) in addition to the polycation, over a period of

36 hours. Control mice are injected with medium collected from confluent dishes of NIH3T3 cells. Following injection of the viral conditioned supernatant, the mice are analyzed for survival as well as tumor growth over time as compared to mock injected controls. Results indicate that treatment of 5 the ovarian cancer occurs. At death, the tumors are removed, weighed, and the cells dissociated for DNA extraction for Southern blot analysis to detect recombinant provirus.

Those skilled in the art will be able to ascertain using no more than routine experimentation, many equivalents of the specific embodiments of the 10 invention described herein. These and all other equivalents are intended to be encompassed by the following claims.

In other embodiments, the invention provides methods and compositions for treating diseases and processes that are mediated by angiogenesis including, but not limited to, hemangioma, solid tumors, leukemia, metastasis, 15 telangiectasia, psoriasis, scleroderma, pyogenic granuloma, myocardial angiogenesis, plaque neovascularization, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, corneal diseases, rubeosis, neovascular glaucoma, diabetic retinopathy, retrobulbar fibroplasia, arthritis, diabetic neovascularization, macular degeneration, wound 20 healing, peptic ulcer, *Helicobacter* related diseases, fractures, keloids, vasculogenesis, hematopoiesis, ovulation, menstruation, placentation, and cat scratch fever.

What is claimed is:

CLAIMS

1. Use of a nucleic acid molecule which expresses an anti-angiogenic polypeptide selected from the group consisting of human angiostatin, murine angiostatin, human endostatin, murine endostatin, and angiogenesis-inhibiting 5 fragments thereof in the preparation of a medicament for inhibiting tumor growth in a human patient harboring a solid tumor, wherein expression of the anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells, thereby inhibiting its 10 growth.

2. Use of a nucleic acid molecule which expresses an anti-angiogenic polypeptide of the formula A-B, wherein

A and B are polypeptide and/or export signal joined by a polypeptide and/or export signal bond;

15 A contains at least amino acids and comprises kringles 1, 2, and 3 of human or murine angiostatin; and

B contains at least amino acids and includes at least 75% of the amino acid sequence of human or murine endostatin in the preparation of a medicament for inhibiting tumor growth in a human patient harboring a solid 20 tumor, wherein expression of the anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells, thereby inhibiting its growth.

3. The use of claim 2, wherein A further comprises kringle region 4 of

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human or murine angiostatin.

4. The use of claim 2 or claim 3, wherein A further comprises kringle 5 of human or murine plasminogen.

5. The use of claim 1 or claim 2, wherein said nucleic acid molecule 5 constitutes a portion of a viral vector.

6. The use of claim 1 or claim 2, wherein said nucleic acid molecule constitutes a portion of a plasmid.

7. The use of claim 6, wherein said plasmid is carried in a cell-free carrier so that the plasmid transfects living cells of the patient following 10 plasmid administration, causing expression of the anti-angiogenesis polypeptide and/or export signal in the patient such that angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells is inhibited, causing inhibition of tumor growth.

15 8. The use of claim 6, wherein said plasmid has been transfected into animal cells *ex vivo*, wherein said animal cells express the anti-angiogenesis polypeptide to inhibit tumor-associated angiogenesis and tumor growth.

9. The use of claim 5, wherein said viral vector is carried in a cell-free carrier, so that the viral vector is incorporated into living cells of the patient 20 following viral vector administration, causing expression of the anti-

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angiogenesis polypeptide in the patient such that angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells is inhibited, causing inhibition of tumor growth.

5 10. The use of claim 5, wherein animal cells are infected with said viral vector *ex vivo* and then administered to said patient, wherein said animal cells express the anti-angiogenesis polypeptide to inhibit tumor-associated angiogenesis and tumor growth.

11. The use of claim 8, wherein said animal cells are human cells.

10 12. The use of claim 11, wherein said human cells are autologous.

13. The use of claim 11, wherein said human cells are allogeneic.

14. The use of claim 10, wherein said animal cells are human cells.

15. The use of claim 14, wherein said human cells are autologous.

16. The use of claim 14, wherein said human cells are allogeneic.

15 17. The use of claim 5, wherein said viral vector is a retroviral vector.

18. The use of claim 5, wherein said viral vector is a non-retroviral vector selected from the group consisting of adenoviral, adeno-associated, herpes, Simliki Forest virus, and poxvirus vectors.

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19. The use of claim 17, wherein said retroviral vector is Murine Stem Cell Virus or a lentivirus.

20. The use of claim 1, wherein said angiostatin comprises kringle 1, 2 and 3.

5 21. The use of claim 20, wherein said angiostatin further comprises kringle 4.

22. The use of claim 1, wherein said anti-angiogenic polypeptide is a fusion of angiostatin or a biologically active fragment thereof and endostatin or a biologically active fragment thereof.

10 23. The use of claim 1, wherein said nucleic acid molecule includes a nucleotide sequence encoding a signal polypeptide and/or export signal for effecting secretion of said anti-angiogenesis polypeptide.

24. The use of claim 23, wherein said signal polypeptide and/or export signal is plasminogen signal polypeptide and/or export signal.

15 25. The use of claim 1, wherein said nucleic acid molecule includes a nucleotide sequence encoding a preactivation polypeptide and/or export signal for effecting Golgi and/or ER export of the anti-angiogenic polypeptide..

20 26. The use of claim 25, wherein said preactivation polypeptide and/or export signal is a preactivation polypeptide and/or export signal of a human protein of the blood coagulation cascade.

27. The use of claim 26, wherein said preactivation polypeptide and/or export signal is human plasminogen preactivation polypeptide and/or export signal.

28. The method of claim 25, wherein the preactivation encoding 5 sequence is positioned between a signal-encoding sequence and the sequence encoding the anti-angiogenic polypeptide and/or export signal.

29. The use of claim 1, wherein said nucleic acid molecule includes a nucleotide sequence encoding a tag for identification of said anti-angiogenic polypeptide.

10 30. The method of claim 27, wherein said tag is a Flag tag polypeptide and/or export signal.

31. A viral gene therapy vector comprising a nucleic acid molecule which encodes an anti-angiogenic polypeptide selected from the group 15 consisting of human angiostatin, murine angiostatin, human endostatin, murine endostatin, and angiogenesis-inhibiting fusions and fragments thereof, wherein said viral vector is sufficiently attenuated for use in human gene therapy.

32. A human cell infected with the vector of claim 31.

33. Use of a nucleic acid molecule which expresses in said patient an anti-angiogenic polypeptide selected from the group consisting of human 20 angiostatin, murine angiostatin, human endostatin, murine endostatin, and angiogenesis-inhibiting fusions and fragments thereof, in the preparation of a

medicament for treating a human patient suffering from diabetic retinopathy, wherein expression of the anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the retina.

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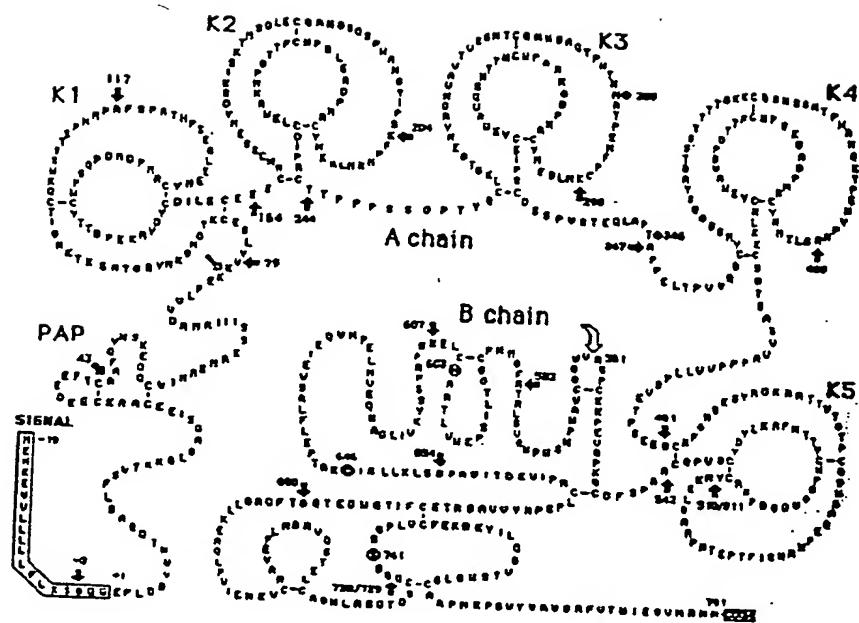


FIG. 1

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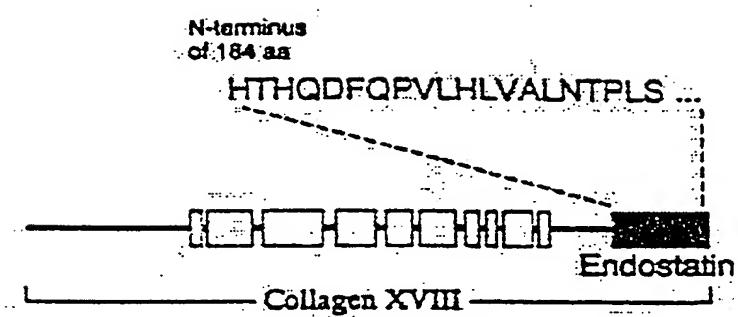
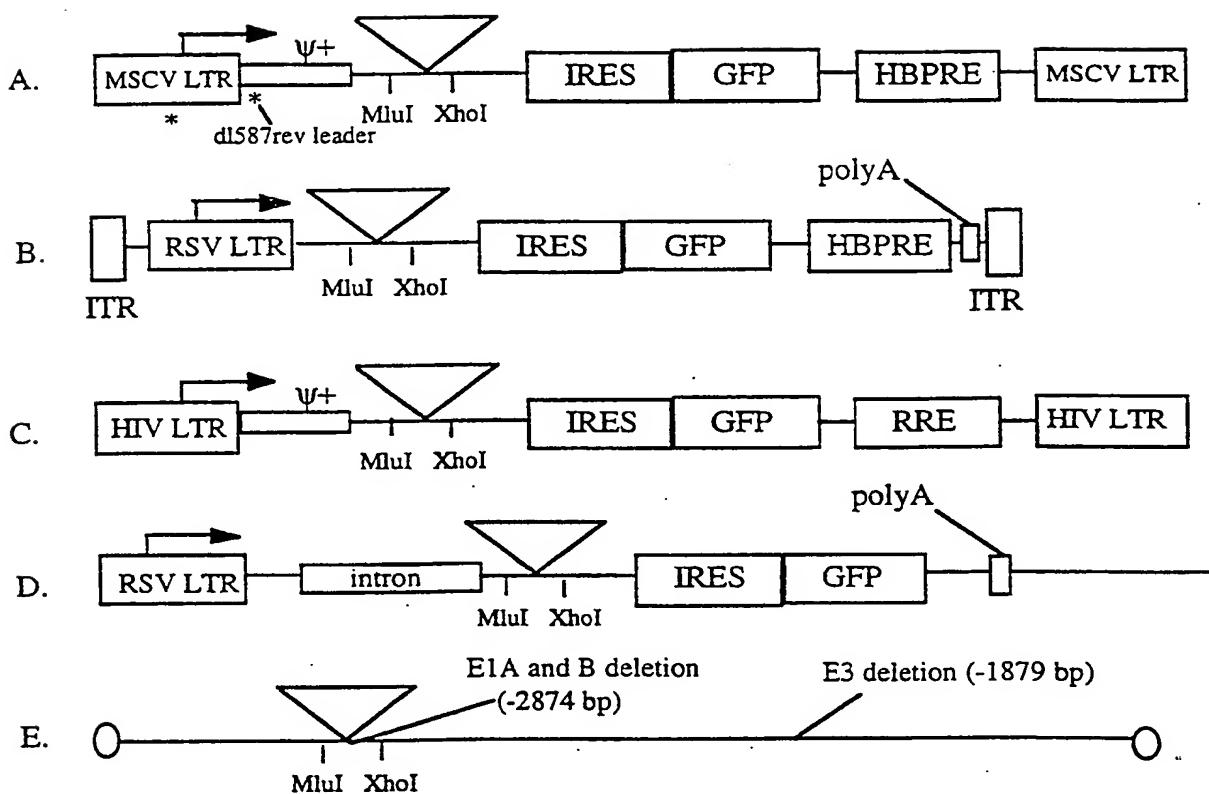
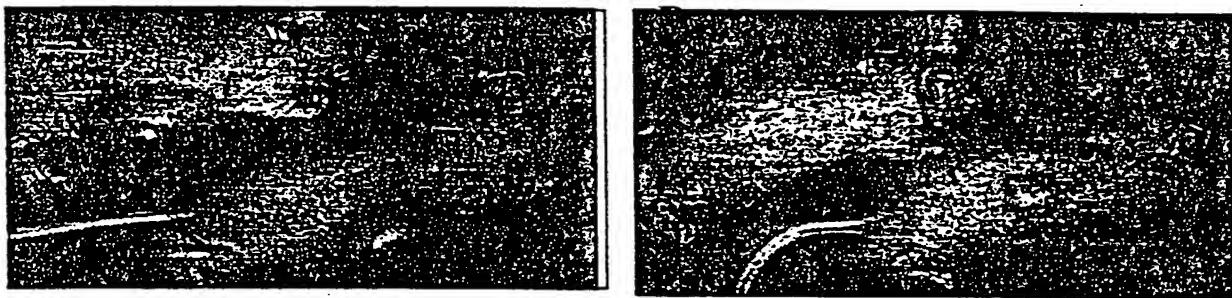


Fig. 2



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17:1

FIG. 4

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signal peptide

precactivation peptide (PAP) human plasminogen

ATGAAACATAAGGAAGTGGTCTCTACTTCTTTATTCCTGAAATCAGGTCAAGGAGAGCCCTGGATGACTATGTAATACCCACGGGCTTCACTGT
MetGluHisLysGluValValLeuLeuLeuLeuLeuLeuLysSerGlyGlnGlyGluProLeuAspAspTyrValAsnThrGlnGlyAlaSerLeuPhe
TCAGTGTCACTAAGAACGGCTGGAGCAGGAAGTATAGAAGAAGATGTCAGCAAAATGTCAGGAGGACGAAGAAATTCACTTCGGTCACTGAGGGCATTCCTCAATATCA
SerValThrLysLysGlnLeuGlyAlaGlySerIleGluGluCysAlaAlaLysCysGluGluAspGluGluPheThrCysArgAlaPheGlnTyrHis
CACTAAAGAGCAACAAATGTCAGTAAATGCGAACAGGAAGTCTCCATAATCATTAGGATGAGAGATGAGTTTATTTGAAAGAAAGTGTATCTC
SerLysGluGlnGlnCysValIleMetAlaGluAsnArgLysSerIleIleArgMetArgAspValValLeuPheGluLysValTyrLeu
TCAGACTGCAAGACTGGAAATGAAAGAACTACAGAGGGACGATGTCACAAACAAAAATGGCATCACCTCTCAAAATGAGTTCCACTCTCCCCACA
SerGluCysLysThrGlyAsnGlyLysAsnTyrArgGlyThrMetSerLysThrLysAsnGlyIleThrCysGlnLysTrpSerSerThrSerProHisArg
GACCTAGATCTCAGCTGGTACACACCCCTCAGAGGGACTGGAGGAGACTACTGCAAGGAACTTCAGACAGACATCGAGGGCCCTGGTGTACTAC
ProArgPheSerProAlaThrHisProSerGluGlyLeuGluIuAsnTyrCysArgAsnProAspAspProGlnGlyProTyrPheCysTyrThrThr
TGATCCAGAAAAGAGATATGACTACTGCGACATCTTGAGTGTCAAGAGGAATGATGTCAGTGGAGAAAATATGACGGCAAATTTCCAAGACC
AspProGluLysArgTyrAspTyrCysAspIleLeuGluCysGluGluGluCysMetHisCysSerGlyGlnAsnTyrAspGlyLysIleSerLysThr
ATGTCCTGGACTGGAAATGCGAGGCTGGACTCTCAGAGCCCACACGCTCATGGATACCTCTTCACAACTGAGAACCTGAGAGAAATTACT
MetSerGlyLeuGluCysGlnAlaTrpAspSerGlnSerProHisAlaHisGlyTyrIleProSerLysPheProAsnLysAsnIleLeuLysLysAsnTyrCys
GTCGTAACCCCGATAGGGAGCTCGGGCTTGTTTACCCACCGGAAACAAAGGGCTGGAAACTTGGGACATCCCCCTGTCACAAACACCTCCACC
ArgAsnProAspArgLysLeuArgProTyrPheCysPheThrAspProAsnLysArgTyrGluLeuCysAspIleProArgCysThrThrProProPro
ATCTCTGGTCCCCACCTAACGAGTGTCTGAAAGGAAACAGCTGAAACTATCGCGGAATGTCGCTGTTACCGTTTCCGGGACACCTGTCAGGACTGGAGT
SerSerGlyProThrTyrGlnCysLeuLysGlyThrGlyGluAsnTyrArgGlyAsnValAlaValThrValSerGlyHisThrCysGlnHisTrpSer
GCACAGACCCCTCACACACATAACAGGACACCCAGAAAATCTCCCTGCAAAATTTGGATGAAAATCTGCGCAATCTGACGGAAAAGGGCCCAT
AlaGlnThrProHisThrHisAsnArgThrProGluAsnProCysLysAsnLeuGluAsnTyrCysArgAsnProAspGlyLysArgAlaProTyr
GGTCCCATACAACAAACAGCCAAGTGGCTGGGAGTACTGTAAGATACCCTGCTGTGACTCTCCCGACTATCCAGGAACAATTGGCTCCACAGCACT
CysHisThrThrAsnSerGlnValArgTrpGluTyrCysLysIleProSerCysAspSerProValSerThrGluGlnLeuAlaProThrAlaPro
ACCTGAGCTAACCCCTGTTGCTCCAGGACTGCTTACCATGTTGATGAGCTACCGAGGACATCTGCGCAACACGAGGAAAGGAGTGTCACT
ProGluLeuThrProValValGlnAspCysTyrHisGlyAspGlyGlnSerTyrArgGlyThrSerSerThrThrGlyLysLysCysGlnSer
TGGTCATCTGACACCACACCCGACAGAACCCCCAGAAAATCTACCCAAATGCTGCGCTGACAATGACTACTGCAAGGAAATCCAGATGGCATAAG
TrpSerMetThrProHisArgHisGlnLysThrProGluAsnTyrProAsnAlaLeuThrMetAsnTyrCysArgAsnProAspAlaAspLysGly
GCCCTGGTTTACACAGACCCAGGGCTGGGAGTACTGCAACCTGAAAATGCTCAGGACAGAACGGACTGTGTAGCACCTCCGCCCTG
ProTyrPheThrThrAspProSerValArgTyrGluTyrCysAsnLeuLysLysCysSerGlyThrGluAlaSerValValAlaProProProVal
TGTCTGGTCCAGATGAGACTCTTCCGGAAAGAGACTGTATCTGGGAATGGAAAGGATAACCSAGGCAAGGGGGGACCACTGTTACTGGGAGC
ValLeuLeuProAspValGluThrProSerGluGluAspCysMetPheGlyAsnGlyLysGlyTyrTyrGlyLysArgAlaThrThrValThrGlyThr
CCATGCCAGGACTGGGCTGCCAGGAGGCCCATAGACACAGCAATTCTCACTCCAGAGACAAATCCACGGGGGTGGAAAATTAATCTGCCGTAA
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end human plasminogen coding sequence

→ start mouse endostatin

mouse endostatin

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end mouse endostatin coding sequence

Fig 6

Tue, Oct 21, 1997
Code: Universal

Mou Plasm cDNA

Page 3

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ProLeuVal

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THEIR USE IN TREATING ANGIOGENESIS-RELATED DISEASES

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Leu	Phe	Ser	Val	Thr	Lys	Lys	Gln	Leu	Gly	Ala	Gly	Ser	Ile	Glu	Glu	
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Cys	Ala	Ala	Lys	Cys	Glu	Glu	Asp	Glu	Glu	Phe	Thr	Cys	Arg	Ala	Phe	
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Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Pro Gln				
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Lys Gly Pro Trp Cys Phe Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr			
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Pro Pro Val Val Leu Leu Pro Asp Val Glu Thr Pro Ser Glu Glu Asp			
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 Leu Phe Ser Ile Thr Lys Lys Gln Leu Ala Ala Gly Gly Val Ser Asp
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 Cys Leu Ala Lys Cys Glu Gly Glu Thr Asp Phe Val Cys Arg Ser Phe
 50 55 60
 cag tac cac agc aaa gag cag caa tgc gtg atc atg gcg gag aac agc 240
 Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Ser
 65 70 75 80
 aag act tcc tcc atc atc cgg atg aga gac gtc atc tta ttc gaa aag 288
 Lys Thr Ser Ser Ile Ile Arg Met Arg Asp Val Ile Leu Phe Glu Lys
 85 90 95
 aga gtg tat ctg tca gaa tgt aag acc ggc atc ggc aac ggc tac aga 336
 Arg Val Tyr Leu Ser Glu Cys Lys Thr Gly Phe Gly Asn Gly Tyr Arg
 100 105 110
 gga acc atg tcc agg aca aag agt ggt gtt gcc tgt caa aag tgg ggt 384
 Gly Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly

115	120	125	
gcc acg ttc ccc cac gta ccc aac tac tct ccc agt aca cat ccc aat Ala Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn 130	135	140	432
gag gga cta gaa gag aac tac tgt agg aac cca gac aat gat gaa caa Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln 145	150	155	480
ggg cct tgg tgc tac act aca gat ccg gac aag aga tat gac tac tgc Gly Pro Trp Cys Tyr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys 165	170	175	528
aac att cct gaa tgt gaa gag gaa tgc atg tac tgc agt gga gaa aag Asn Ile Pro Glu Cys Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys 180	185	190	576
tat gag ggc aaa atc tcc aag acc atg tct gga ctt gac tgc cag gcc Tyr Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala 195	200	205	624
tgg gat tct cag agc cca cat gct cat gga tac atc cct gcc aaa ttt Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe 210	215	220	672
cca agc aag aac ctg aag atg aat tat tgc cac aac cct gac ggg gag Pro Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu 225	230	235	720
cca agg ccc tgg tgc ttc aca aca gac ccc acc aaa cgc tgg gaa tac Pro Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr 245	250	255	768
tgt gac atc ccc cgc tgc aca aca ccc ccg ccc cca ccc agc cca acc Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Ser Pro Thr 260	265	270	816
tac caa tgt ctg aaa gga aga ggt gaa aat tac cga ggg acc gtg tct Tyr Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser 275	280	285	864
gtc acc gtg tct ggg aaa acc tgt cag cgc tgg agt gag caa acc cct Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro 290	295	300	912
cat agg cac aac agg aca cca gaa aat ttc ccc tgc aaa aat ctg gaa His Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu 305	310	315	960
gag aac tac tgc cgg aac cca gat gga gaa act gct ccc tgg tgc tat Glu Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr 325	330	335	1008
acc act gac agc cag ctg agg tgg gag tac tgt gag att cca tcc tgc			1056

Thr	Thr	Asp	Ser	Gln	Leu	Arg	Trp	Glu	Tyr	Cys	Glu	Ile	Pro	Ser	Cys	
				340				345				350				
gag tcc tca gca tca cca gac cag tca gat tcc tca gtt cca cca gag															1104	
Glu	Ser	Ser	Ala	Ser	Pro	Asp	Gln	Ser	Asp	Ser	Ser	Val	Pro	Pro	Glu	
			355				360				365					
gag caa aca cct gtg gtc cag gaa tgc tac cag agc gat ggg cag agc															1152	
Glu	Gln	Thr	Pro	Val	Val	Gln	Glu	Cys	Tyr	Gln	Ser	Asp	Gly	Gln	Ser	
			370				375				380					
tat cgg ggt aca tcg tcc act acc atc aca ggg aag aag tgc cag tcc															1200	
Tyr	Arg	Gly	Thr	Ser	Ser	Thr	Thr	Ile	Thr	Gly	Lys	Lys	Cys	Gln	Ser	
			385				390				395			400		
tgg gca gct atg ttt cca cac agg cat tcg aag acc cca gag aac ttc															1248	
Trp	Ala	Ala	Met	Phe	Pro	His	Arg	His	Ser	Lys	Thr	Pro	Glu	Asn	Phe	
			405				410				415					
cca gat gct ggc ttg gag atg aac tac tgc agg aac ccg gat ggt gac															1296	
Pro	Asp	Ala	Gly	Leu	Glu	Met	Asn	Tyr	Cys	Arg	Asn	Pro	Asp	Gly	Asp	
			420				425				430					
aag ggc cct tgg tgc tac acc act gac ccg agc gtc agg tgg gaa tac															1344	
Lys	Gly	Pro	Trp	Cys	Tyr	Thr	Asp	Pro	Ser	Val	Arg	Trp	Glu	Tyr		
			435				440				445					
tgc aac ctg aag cgg tgc tca gag aca gga ggg agt gtt gtg gaa ttg															1392	
Cys	Asn	Leu	Lys	Arg	Cys	Ser	Glu	Thr	Gly	Gly	Ser	Val	Val	Glu	Leu	
			450				455				460					
ccc aca gtt tcc cag gaa cca agt ggg ccg agc gac tct gag aca gac															1440	
Pro	Thr	Val	Ser	Gln	Glu	Pro	Ser	Gly	Pro	Ser	Asp	Ser	Glu	Thr	Asp	
			465				470				475			480		
tgc atg tat ggg aat ggc aaa gac tat cgg ggc aaa acg gcc gtc act															1488	
Cys	Met	Tyr	Gly	Asn	Gly	Lys	Asp	Tyr	Arg	Gly	Lys	Thr	Ala	Val	Thr	
			485				490				495					
gca gct ggc acc ccc tgc cag gga tgg gct gcc cag gag ccc cac agg															1536	
Ala	Ala	Gly	Thr	Pro	Cys	Gln	Gly	Trp	Ala	Ala	Gln	Glu	Pro	His	Arg	
			500				505				510					
cac agc atc ttc acc cca cag aca aac cca cgg gca gat ctg gaa aag															1584	
His	Ser	Ile	Phe	Thr	Pro	Gln	Thr	Asn	Pro	Arg	Ala	Asp	Leu	Glu	Lys	
			515				520				525					
aac tac tgc cga aac cca gat ggg gat gtg aat ggt cct tgg tgc tat															1632	
Asn	Tyr	Cys	Arg	Asn	Pro	Asp	Gly	Asp	Val	Asn	Gly	Pro	Trp	Cys	Tyr	
			530				535				540					
aca aca aac ccc aga aaa ctt tat gac tat tgt gac atc ccc ctg tgt															1680	
Thr	Thr	Asn	Pro	Arg	Lys	Leu	Tyr	Asp	Tyr	Cys	Asp	Ile	Pro	Leu	Cys	
			545				550				555			560		

gca tca gca tca tcc ttt gag tgc ggg aaa cct cag gtg gaa ccg aag Ala Ser Ala Ser Ser Phe Glu Cys Gly Lys Pro Gln Val Glu Pro Lys 565 570 575	1728
aaa tgc cct ggg agg gtg gtg ggt ggc tgc gtg gcc aac cct cac tcc Lys Cys Pro Gly Arg Val Val Gly Cys Val Ala Asn Pro His Ser 580 585 590	1776
tgg ccc tgg caa atc agc ctt aga aca aga ttt acc gga cag cac ttc Trp Pro Trp Gln Ile Ser Leu Arg Thr Arg Phe Thr Gly Gln His Phe 595 600 605	1824
tgt ggc ggt act tta ata gcc cca gag tgg gtt ctg act gct gcc cac Cys Gly Gly Thr Leu Ile Ala Pro Glu Trp Val Leu Thr Ala Ala His 610 615 620	1872
tgt ttg gag aaa tct tca aga cct gaa ttc tac aag gtt atc ctg ggt Cys Leu Glu Lys Ser Ser Arg Pro Glu Phe Tyr Lys Val Ile Leu Gly 625 630 635 640	1920
gcg cac gaa gaa tat atc cgt ggg ttg gat gtt cag gaa ata tca gta Ala His Glu Glu Tyr Ile Arg Gly Leu Asp Val Gln Glu Ile Ser Val 645 650 655	1968
gcc aaa ctg atc ttg gag ccc aac aac cgt gac att gcc ctg ctg aaa Ala Lys Leu Ile Leu Glu Pro Asn Asn Arg Asp Ile Ala Leu Leu Lys 660 665 670	2016
cta agc cgc cca gcc acc atc acg gat aaa gtc att cca gct tgt ctg Leu Ser Arg Pro Ala Thr Ile Thr Asp Lys Val Ile Pro Ala Cys Leu 675 680 685	2064
cca tct cca aat tac atg gtt gct gac cgg aca ata tgt tac atc acc Pro Ser Pro Asn Tyr Met Val Ala Asp Arg Thr Ile Cys Tyr Ile Thr 690 695 700	2112
ggc tgg gga gag act caa ggg act ttc ggt gcc ggt cgt ctc aag gag Gly Trp Gly Glu Thr Gln Gly Thr Phe Gly Ala Gly Arg Leu Lys Glu 705 710 715 720	2160
gct cag ctg cct gtg att gag aac aag gtg tgc aac cgc gtc gag tat Ala Gln Leu Pro Val Ile Glu Asn Lys Val Cys Asn Arg Val Glu Tyr 725 730 735	2208
ctg aac aac aga gtc aaa tcc acg gag ctc tgt gcc ggg caa ctg gct Leu Asn Asn Arg Val Lys Ser Thr Glu Leu Cys Ala Gly Gln Leu Ala 740 745 750	2256
ggc gtc gac agc tgc caa ggc gac agt gga gga cct ctg gtt tgc Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys 755 760 765	2304
tcc gag aag gac aag tac att tta caa gga gtc act tct tgg ggt ctt Phe Glu Lys Asp Lys Tyr Ile Leu Gln Gly Val Thr Ser Trp Gly Leu 770 775 780	2352

ggc tgt gct cgc ccc aat aag cct ggt gtc tac gtt cgt gtc tca cgg 2400
 Gly Cys Ala Arg Pro Asn Lys Pro Gly Val Tyr Val Arg Val Ser Arg
 785 790 795 800

ttt gtt gat tgg att gaa agg gag atg agg aat aac tgacttaggtg 2446
 Phe Val Asp Trp Ile Glu Arg Glu Met Arg Asn Asn
 805 810

gaaggccgag caaaacctct gcttactaaa gcttactgaa tatggggaga gggcttaggg 2506
 tgtttgaaa aactgacagt aatcaaactg ggacactaca ctgaaccaca gcttcctgttc 2566
 gccccctcagc ccctccccctt ttttgtatt attgtgggta aaatttcct gtctgtggac 2626
 ttctgattt tgtgacaata gaccatcaact gctgtgaccc ttgttggaaa taaaactcgat 2686
 acttactttg 2696

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 <211> 812
 <212> PRT
 <213> Mus musculus

<400> 4
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 Gly Gln Gly Asp Ser Leu Asp Gly Tyr Ile Ser Thr Gln Gly Ala Ser
 20 25 30
 Leu Phe Ser Leu Thr Lys Lys Gln Leu Ala Ala Gly Gly Val Ser Asp
 35 40 45
 Cys Leu Ala Lys Cys Glu Gly Glu Thr Asp Phe Val Cys Arg Ser Phe
 50 55 60
 Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Ser
 65 70 75 80
 Lys Thr Ser Ser Ile Ile Arg Met Arg Asp Val Ile Leu Phe Glu Lys
 85 90 95
 Arg Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg
 100 105 110
 Gly Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly
 115 120 125
 Ala Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn
 130 135 140
 Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln
 145 150 155 160
 Gly Pro Trp Cys Tyr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys
 165 170 175
 Asn Ile Pro Glu Cys Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys
 180 185 190
 Tyr Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala
 195 200 205
 Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe
 210 215 220
 Pro Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu
 225 230 235 240
 Pro Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr
 245 250 255
 Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Pro Ser Pro Thr
 260 265 270

Tyr Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser
 275 280 285
 Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro
 290 295 300
 His Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu
 305 310 315 320
 Glu Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr
 325 330 335
 Thr Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys
 340 345 350
 Glu Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu
 355 360 365
 Glu Gln Thr Pro Val Val Gln Glu Cys Tyr Gln Ser Asp Gly Gln Ser
 370 375 380
 Tyr Arg Gly Thr Ser Ser Thr Ile Thr Gly Lys Lys Cys Gln Ser
 385 390 395 400
 Trp Ala Ala Met Phe Pro His Arg His Ser Lys Thr Pro Glu Asn Phe
 405 410 415
 Pro Asp Ala Gly Leu Glu Met Asn Tyr Cys Arg Asn Pro Asp Gly Asp
 420 425 430
 Lys Gly Pro Trp Cys Tyr Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr
 435 440 445
 Cys Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly Ser Val Val Glu Leu
 450 455 460
 Pro Thr Val Ser Gln Glu Pro Ser Gly Pro Ser Asp Ser Glu Thr Asp
 465 470 475 480
 Cys Met Tyr Gly Asn Gly Lys Asp Tyr Arg Gly Lys Thr Ala Val Thr
 485 490 495
 Ala Ala Gly Thr Pro Cys Gln Gly Trp Ala Ala Gln Glu Pro His Arg
 500 505 510
 His Ser Ile Phe Thr Pro Gln Thr Asn Pro Arg Ala Asp Leu Glu Lys
 515 520 525
 Asn Tyr Cys Arg Asn Pro Asp Gly Asp Val Asn Gly Pro Trp Cys Tyr
 530 535 540
 Thr Thr Asn Pro Arg Lys Leu Tyr Asp Tyr Cys Asp Ile Pro Leu Cys
 545 550 555 560
 Ala Ser Ala Ser Ser Phe Glu Cys Gly Lys Pro Gln Val Glu Pro Lys
 565 570 575
 Lys Cys Pro Gly Arg Val Val Gly Gly Cys Val Ala Asn Pro His Ser
 580 585 590
 Trp Pro Trp Gln Ile Ser Leu Arg Thr Arg Phe Thr Gly Gln His Phe
 595 600 605
 Cys Gly Gly Thr Leu Ile Ala Pro Glu Trp Val Leu Thr Ala Ala His
 610 615 620
 Cys Leu Glu Lys Ser Ser Arg Pro Glu Phe Tyr Lys Val Ile Leu Gly
 625 630 635 640
 Ala His Glu Glu Tyr Ile Arg Gly Leu Asp Val Gln Glu Ile Ser Val
 645 650 655
 Ala Lys Leu Ile Leu Glu Pro Asn Asn Arg Asp Ile Ala Leu Leu Lys
 660 665 670
 Leu Ser Arg Pro Ala Thr Ile Thr Asp Lys Val Ile Pro Ala Cys Leu
 675 680 685
 Pro Ser Pro Asn Tyr Met Val Ala Asp Arg Thr Ile Cys Tyr Ile Thr
 690 695 700
 Gly Trp Gly Glu Thr Gln Gly Thr Phe Gly Ala Gly Arg Leu Lys Glu

705	710	715	720												
Ala	Gln	Leu	Pro	Val	Ile	Glu	Asn	Lys	Val	Cys	Asn	Arg	Val	Glu	Tyr
725	730	735													
Leu	Asn	Asn	Arg	Val	Lys	Ser	Thr	Glu	Leu	Cys	Ala	Gly	Gln	Leu	Ala
740	745	750													
Gly	Gly	Val	Asp	Ser	Cys	Gln	Gly	Asp	Ser	Gly	Gly	Pro	Leu	Val	Cys
755	760	765													
Phe	Glu	Lys	Asp	Lys	Tyr	Ile	Leu	Gln	Gly	Val	Thr	Ser	Trp	Gly	Leu
770	775	780													
Gly	Cys	Ala	Arg	Pro	Asn	Lys	Pro	Gly	Val	Tyr	Val	Arg	Val	Ser	Arg
785	790	795	800												
Phe	Val	Asp	Trp	Ile	Glu	Arg	Glu	Met	Arg	Asn	Asn				
805	810														

<210> 5
 <211> 1083
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1) ... (1083)

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Tyr	Leu	Ser	Glu	Cys	Lys	Thr	Gly	Asn	Gly	Lys	Asn	Tyr	Arg	Gly	Thr
1	5	10	15												
atg tcc aaa aca aaa aat ggc atc acc tgt caa aaa tgg agt tcc act															
Met	Ser	Lys	Thr	Lys	Asn	Gly	Ile	Thr	Cys	Gln	Lys	Trp	Ser	Ser	Thr
20	25	30													
tct ccc cac aga cct aga ttc tca cct gct aca cac ccc tca gag gga															
Ser	Pro	His	Arg	Pro	Arg	Phe	Ser	Pro	Ala	Thr	His	Pro	Ser	Glu	Gly
35	40	45													
ctg gag gag aac tac tgc agg aat cca gac aac gat ccg cag ggg ccc															
Leu	Glu	Glu	Asn	Tyr	Cys	Arg	Asn	Pro	Asp	Asn	Asp	Pro	Gln	Gly	Pro
50	55	60													
tgg tgc tat act act gat cca gaa aag aga tat gac tac tgc gac att															
Trp	Cys	Tyr	Thr	Asp	Pro	Glu	Lys	Arg	Tyr	Asp	Tyr	Cys	Asp	Ile	
65	70	75	80												
ctt gag tgt gaa gag gaa tgt atg cat tgc agt gga gaa aac tat gac															
Leu	Glu	Cys	Glu	Glu	Cys	Met	His	Cys	Ser	Gly	Glu	Asn	Tyr	Asp	
85	90	95													
ggc aaa att tcc aag acc atg tct gga ctg gaa tgc cag gcc tgg gac															
Gly	Lys	Ile	Ser	Lys	Thr	Met	Ser	Gly	Leu	Glu	Cys	Gln	Ala	Trp	Asp
100	105	110													
tct cag agc cca. gac. gat. gca. tac att .ccat. gca. aac															
Ser	Gln	Ser	Pro	His	Ala	His	Gly	Tyr	Ile	Pro	Ser	Lys	Phe	Pro	Asn
115	120	125													

384.00 100.00

aag aac ctg aag aag aat tac tgt cgt aac ccc gat agg gag ctg cgg	432
Lys Asn Leu Lys Lys Asn Tyr Cys Arg Asn Pro Asp Arg Glu Leu Arg	
130 135 140	
cct tgg tgt ttc acc acc gac ccc aac aag cgc tgg gaa ctt tgc gac	480
Pro Trp Cys Phe Thr Thr Asp Pro Asn Lys Arg Trp Glu Leu Cys Asp	
145 150 155 160	
atc ccc cgc tgc aca aca cct cca cca tct tct ggt ccc acc tac cag	528
Ile Pro Arg Cys Thr Thr Pro Pro Ser Ser Gly Pro Thr Tyr Gln	
165 170 175	
tgt ctg aag gga aca ggt gaa aac tat cgc ggg aat gtg gct gtt acc	576
Cys Leu Lys Gly Thr Gly Glu Asn Tyr Arg Gly Asn Val Ala Val Thr	
180 185 190	
gtt tcc ggg cac acc tgt cag cac tgg agt gca cag acc cct cac aca	624
Val Ser Gly His Thr Cys Gln His Trp Ser Ala Gln Thr Pro His Thr	
195 200 205	
cat aac agg aca cca gaa aac ttc ccc tgc aaa aat ttg gat gaa aac	672
His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Asp Glu Asn	
210 215 220	
tac tgc cgc aat cct gac gga aaa agg gcc cca tgg tgc cat aca acc	720
Tyr Cys Arg Asn Pro Asp Gly Lys Arg Ala Pro Trp Cys His Thr Thr	
225 230 235 240	
aac agc caa gtg cgg tgg gag tac tgt aag ata ccg tcc tgt gac tcc	768
Asn Ser Gln Val Arg Trp Glu Tyr Cys Lys Ile Pro Ser Cys Asp Ser	
245 250 255	
tcc cca gta tcc acg gaa caa ttg gct ccc aca gca cca cct gag cta	816
Ser Pro Val Ser Thr Glu Gln Leu Ala Pro Thr Ala Pro Pro Glu Leu	
260 265 270	
acc cct gtg gtc cag gac tgc tac cat ggt gat gga cag agc tac cga	864
Thr Pro Val Val Gln Asp Cys Tyr His Gly Asp Gly Gln Ser Tyr Arg	
275 280 285	
ggc aca tcc tcc acc acc aca gga aag aag tgt cag tct tgg tca	912
Gly Thr Ser Ser Thr Thr Thr Gly Lys Lys Cys Gln Ser Trp Ser	
290 295 300	
tct atg aca cca cac cgg cac cag aag acc cca gaa aac tac cca aat	960
Ser Met Thr Pro His His Gln Lys Thr Pro Glu Asn Tyr Pro Asn	
305 310 315 320	
gct ggc ctg aca atg aac tac tgc agg aat cca gat gcc gat aaa ggc	1008
Ala Gly Leu Thr Met Asn Tyr Cys Arg Asn Pro Asp Ala Asp Lys Gly	
325 330 335	
ccc tgg tgt ttt acc aca gac ccc agc gtc agg tgg gag tac tgc aac	1056
Pro Trp Cys Phe Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr Cys Asn	

340

345

350

ctg aaa aaa tgc tca gga aca gaa gcg
 Leu Lys Lys Cys Ser Gly Thr Glu Ala
 355 360

1083

<210> 6
 <211> 361
 <212> PRT
 <213> Homo sapiens

<400> 6
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 Met Ser Lys Thr Lys Asn Gly Ile Thr Cys Gln Lys Trp Ser Ser Thr
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 Ser Pro His Arg Pro Arg Phe Ser Pro Ala Thr His Pro Ser Glu Gly
 35 40 45
 Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Pro Gln Gly Pro
 50 55 60
 Trp Cys Tyr Thr Thr Asp Pro Glu Lys Arg Tyr Asp Tyr Cys Asp Ile
 65 70 75 80
 Leu Glu Cys Glu Glu Cys Met His Cys Ser Gly Glu Asn Tyr Asp
 85 90 95
 Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Glu Cys Gln Ala Trp Asp
 100 105 110
 Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ser Lys Phe Pro Asn
 115 120 125
 Lys Asn Leu Lys Lys Asn Tyr Cys Arg Asn Pro Asp Arg Glu Leu Arg
 130 135 140
 Pro Trp Cys Phe Thr Thr Asp Pro Asn Lys Arg Trp Glu Leu Cys Asp
 145 150 155 160
 Ile Pro Arg Cys Thr Thr Pro Pro Pro Ser Ser Gly Pro Thr Tyr Gln
 165 170 175
 Cys Leu Lys Gly Thr Gly Glu Asn Tyr Arg Gly Asn Val Ala Val Thr
 180 185 190
 Val Ser Gly His Thr Cys Gln His Trp Ser Ala Gln Thr Pro His Thr
 195 200 205
 His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Asp Glu Asn
 210 215 220
 Tyr Cys. Arg. Asn. Pro. Asp. Gly. Lys Arg. Ala. Pro. Trp. Cys. His. Thr. Thr
 225 230 235 240
 Asn Ser Gln Val Arg Trp Glu Tyr Cys Lys Ile Pro Ser Cys Asp Ser
 245 250 255
 Ser Pro Val Ser Thr Glu Gln Leu Ala Pro Thr Ala Pro Pro Glu Leu
 260 265 270
 Thr Pro Val Val Gln Asp Cys Tyr His Gly Asp Gly Gln Ser Tyr Arg
 275 280 285
 Gly Thr Ser Ser Thr Thr Thr Gly Lys Lys Cys Gln Ser Trp Ser
 290 295 300
 Ser Met Thr Pro His Arg His Gln Lys Thr Pro Glu Asn Tyr Pro Asn
 305 310 315 320 325
 Ala Gly Leu Thr Met Asn Tyr Cys Arg Asn Pro Asp Ala Asp Lys Gly
 325 330 335

Pro Trp Cys Phe Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr Cys Asn
 340 345 350
 Leu Lys Lys Cys Ser Gly Thr Glu Ala
 355 360

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 <211> 1086
 <212> DNA
 <213> Mus musculus

<220>
 <221> CDS
 <222> (1)...(1086)

<400> 7

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 Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg Gly
 1 5 10 15

acc atg tcc agg aca aag agt ggt gtt gcc tgt caa aag tgg ggt gcc 96
 Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly Ala
 20 25 30

acg ttc ccc cac gta ccc aac tac tct ccc agt aca cat ccc aat gag 144
 Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn Glu
 35 40 45

gga cta gaa gag aac tac tgt agg aac cca gac aat gat gaa caa ggg 192
 Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln Gly
 50 55 60

cct tgg tgc tac act aca gat ccg gac aag aga tat gac tac tgc aac 240
 Pro Trp Cys Tyr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys Asn
 65 70 75 80

att cct gaa tgt gaa gag gaa tgc atg tac tgc agt gga gaa aag tat 288
 Ile Pro Glu Cys Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys Tyr
 85 90 95

gag ggc aaa atc tcc aag acc atg tct gga ctt gac tgc cag gcc tgg 336
 Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala Trp
 100 105 110

gat tct cag agc cca cat gct cat gga tac atc cct gcc aaa ttt cca 384
 Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe Pro
 115 120 125

agc aag aac ctg aag atg aat tat tgc cac aac cct gac ggg gag cca 432
 Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu Pro
 130 135 140

agg ccc tgg tgc ttc aca aca gac ccc acc aaa cgc tgg gaa tac tgt 480
 Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr Cys
 145 150 155 160

gac atc ccc cgc tgc aca aca ccc ccg ccc cca ccc agc cca acc tac	528
Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Pro Ser Pro Thr Tyr	
165 170 175	
caa tgt ctg aaa gga aga ggt gaa aat tac cga ggg acc gtg tct gtc	576
Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser Val	
180 185 190	
acc gtg tct ggg aaa acc tgt cag cgc tgg agt gag caa acc cct cat	624
Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro His	
195 200 205	
agg cac aac agg aca cca gaa aat ttc ccc tgc aaa aat ctg gaa gag	672
Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu Glu	
210 215 220	
aac tac tgc cgg aac cca gat gga gaa act gct ccc tgg tgc tat acc	720
Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr Thr	
225 230 235 240	
act gac agc cag ctg agg tgg gag tac tgt gag att cca tcc tgc gag	768
Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys Glu	
245 250 255	
tcc tca gca tca cca gac cag tca gat tcc tca gtt cca cca gag gag	816
Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu Glu	
260 265 270	
caa aca cct gtg gtc cag gaa tgc tac cag agc gat ggg cag agc tat	864
Gln Thr Pro Val Val Gln Glu Cys Tyr Gln Ser Asp Gly Gln Ser Tyr	
275 280 285	
cgg ggt aca tcg tcc act acc atc aca ggg aag aag tgc cag tcc tgg	912
Arg Gly Thr Ser Ser Thr Thr Ile Thr Gly Lys Lys Cys Gln Ser Trp	
290 295 300	
gca gct atg ttt cca cac agg cat tcg aag acc cca gag aac ttc cca	960
Ala Ala Met Phe Pro His Arg His Ser Lys Thr Pro Glu Asn Phe Pro	
305 310 315 320	
gat gct ggc ttg gag atg aac tac tgc agg aac ccg gat ggt gac aag	1008
Asp Ala Gly Leu Glu Met Asn Tyr Cys Arg Asn Pro Asp Gly Asp, Lys	
325 330 335	
ggc cct tgg tgc tac acc act gac ccg agc gtc agg tgg gaa tac tgc	1056
Gly Pro Trp Cys Tyr Thr Asp Pro Ser Val Arg Trp Glu Tyr Cys	
340 345 350	
aac ctg aag cgg tgc tca gag aca gga ggg	1086
Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly	
355 360	

<210> 8

<211> 362

<212> PRT
 <213> *Mus musculus*

<400> 8
 Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg Gly
 1 5 10 15
 Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly Ala
 20 25 30
 Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn Glu
 35 40 45
 Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln Gly
 50 55 60
 Pro Trp Cys Tyr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys Asn
 65 70 75 80
 Ile Pro Glu Cys Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys Tyr
 85 90 95
 Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala Trp
 100 105 110
 Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe Pro
 115 120 125
 Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu Pro
 130 135 140
 Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr Cys
 145 150 155 160
 Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Ser Pro Thr Tyr
 165 170 175
 Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser Val
 180 185 190
 Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro His
 195 200 205
 Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu Glu
 210 215 220
 Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr Thr
 225 230 235 240
 Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys Glu
 245 250 255
 Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu Glu
 260 265 270
 Gln Thr Pro Val Val Gln Glu Cys Tyr Gln Ser Asp Gly Gln Ser Tyr
 275 280 285
 Arg Gly Thr Ser Ser Thr Thr Ile Thr Gly Lys Lys Cys Gln Ser Trp
 290 295 300
 Ala Ala Met Phe Pro His Arg His Ser Lys Thr Pro Glu Asn Phe Pro
 305 310 315 320
 Asp Ala Gly Leu Glu Met Asn Tyr Cys Arg Asn Pro Asp Gly Asp Lys
 325 330 335
 Gly Pro Trp Cys Tyr Thr Asp Pro Ser Val Arg Trp Glu Tyr Cys
 340 345 350
 Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly
 355 360

<210> 9
 <211> 552
 <212> DNA
 <213> *Mus musculus*

<220>
 <221> CDS
 <222> (1) ... (552)

<400> 9
 cat act cat cag gac ttt cag cca gtg ctc cac ctg gtg gca ctg aac 48
 His Thr His Gln Asp Phe Gln Pro Val Leu His Leu Val Ala Leu Asn
 1 5 10 15
 acc ccc ctg tct gga ggc atg cgt ggt atc cgt gga gca gat ttc cag 96
 Thr Pro Leu Ser Gly Gly Met Arg Gly Ile Arg Gly Ala Asp Phe Gln
 20 25 30
 tgc ttc cag caa gcc cga gcc gtg ggg ctg tcg ggc acc ttc cgg gct 144
 Cys Phe Gln Gln Ala Arg Ala Val Gly Leu Ser Gly Thr Phe Arg Ala
 35 40 45
 ttc ctg tcc tct agg ctg cag gat ctc tat agc atc gtg cgc cgt gct 192
 Phe Leu Ser Ser Arg Leu Gln Asp Leu Tyr Ser Ile Val Arg Arg Ala
 50 55 60
 gac cgg ggg tct gtg ccc atc gtc aac ctg aag gac gag gtg cta tct 240
 Asp Arg Gly Ser Val Pro Ile Val Asn Leu Lys Asp Glu Val Leu Ser
 65 70 75 80
 ccc agc tgg gac tcc ctg ttt tct ggc tcc cag ggt caa gtg caa ccc 288
 Pro Ser Trp Asp Ser Leu Phe Ser Gly Ser Gln Gly Gln Val Gln Pro
 85 90 95
 ggg gcc cgc atc ttt tct ttt gac ggc aga gat gtc ctg aga cac cca 336
 Gly Ala Arg Ile Phe Ser Phe Asp Gly Arg Asp Val Leu Arg His Pro
 100 105 110
 gcc tgg ccg cag aag agc gta tgg cac ggc tcg gac ccc agt ggg cgg 384
 Ala Trp Pro Gln Lys Ser Val Trp His Gly Ser Asp Pro Ser Gly Arg
 115 120 125
 agg ctg atg gag agt tac tgt gag aca tgg cga act gaa act act ggg 432
 Arg Leu Met Glu Ser Tyr Cys Glu Thr Trp Arg Thr Glu Thr Thr Gly
 130 135 140
 gct aca ggt cag gcc tcc ctg ctg tca ggc agg ctc ctg gaa cag 480
 Ala Thr Gly Gln Ala Ser Ser Leu Leu Ser Gly Arg Leu Leu Glu Gln
 145 150 155 160
 aaa gct gcg agc tgc cac aac agc tac atc gtc ctg tgc att gag aat 528
 Lys Ala Ala Ser Cys His Asn Ser Tyr Ile Val Leu Cys Ile Glu Asn
 165 170 175
 agc ttc atg acc tct ttc tcc aaa 552
 Ser Phe Met Thr Ser Phe Ser Lys
 180

<210> 10

<211> 184
 <212> PRT
 <213> Mus musculus

<400> 10
 His Thr His Gln Asp Phe Gln Pro Val Leu His Leu Val Ala Leu Asn
 1 5 10 15
 Thr Pro Leu Ser Gly Gly Met Arg Gly Ile Arg Gly Ala Asp Phe Gln
 20 25 30
 Cys Phe Gln Gln Ala Arg Ala Val Gly Leu Ser Gly Thr Phe Arg Ala
 35 40 45
 Phe Leu Ser Ser Arg Leu Gln Asp Leu Tyr Ser Ile Val Arg Arg Ala
 50 55 60
 Asp Arg Gly Ser Val Pro Ile Val Asn Leu Lys Asp Glu Val Leu Ser
 65 70 75 80
 Pro Ser Trp Asp Ser Leu Phe Ser Gly Ser Gln Gly Gln Val Gln Pro
 85 90 95
 Gly Ala Arg Ile Phe Ser Phe Asp Gly Arg Asp Val Leu Arg His Pro
 100 105 110
 Ala Trp Pro Gln Lys Ser Val Trp His Gly Ser Asp Pro Ser Gly Arg
 115 120 125
 Arg Leu Met Glu Ser Tyr Cys Glu Thr Trp Arg Thr Glu Thr Thr Gly
 130 135 140
 Ala Thr Gly Gln Ala Ser Ser Leu Leu Ser Gly Arg Leu Leu Glu Gln
 145 150 155 160
 Lys Ala Ala Ser Cys His Asn Ser Tyr Ile Val Leu Cys Ile Glu Asn
 165 170 175
 Ser Phe Met Thr Ser Phe Ser Lys
 180

<210> 11
 <211> 1414
 <212> DNA
 <213> Mus musculus

<220>
 <221> CDS
 <222> (1) ... (1414)

<400> 11
 atg gac cat aag gaa gta atc ctt ctg ttt ctc ttg ctt ctg aaa cca 48
 Met Asp His Lys Glu Val Ile Leu Leu Phe Leu Leu Leu Lys Pro
 1 5 10 15
 gga caa ggg gac tcg ctg gat ggc tac ata agc aca caa ggg gct tca 96
 Gly Gln Gly Asp Ser Leu Asp Gly Tyr Ile Ser Thr Gln Gly Ala Ser
 20 25 30
 ctg ttc agt ctc acc aag aag cag ctc gca gca gga ggt gtc tcg gac 144
 Leu Phe Ser Leu Thr Lys Lys Gln Leu Ala Ala Gly Gly Val Ser Asp
 35 40 45
 tgt ttg gcc aaa tgt gaa ggg gaa aca gac ttt gtc tgc agg tca ttc 192
 Cys Leu Ala Lys Cys Glu Gly Glu Thr Asp Phe Val Cys Arg Ser Phe
 50 55 60

cag tac cac agc aaa gag cag caa tgc gtg atc atg gcg gag aac agc Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Ser 65 70 75 80	240
aag act tcc tcc atc atc cgg atg aga gac gtc atc tta ttc gaa aag Lys Thr Ser Ser Ile Ile Arg Met Arg Asp Val Ile Leu Phe Glu Lys 85 90 95	288
aga gtg tat ctg tca gaa tgt aag acc ggc atc ggc aac ggc tac aga Arg Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg 100 105 110	336
gga acc atg tcc agg aca aag agt ggt gtt gcc tgt caa aag tgg ggt Gly Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly 115 120 125	384
gcc acg ttc ccc cac gta ccc aac tac tct ccc agt aca cat ccc aat Ala Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn 130 135 140	432
gag gga cta gaa gag aac tac tgt agg aac cca gac aat gat gaa caa Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln 145 150 155 160	480
ggg cct tgg tgc tac act aca gat ccg gac aag aga tat gac tac tgc Gly Pro Trp Cys Tyr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys 165 170 175	528
aac att cct gaa tgt gaa gag gaa tgc atg tac tgc agt gga gaa aag Asn Ile Pro Glu Cys Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys 180 185 190	576
tat gag ggc aaa atc tcc aag acc atg tct gga ctt gac tgc cag gcc Tyr Glu Gly Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala 195 200 205	624
tgg gat tct cag agc cca cat gct cat gga tac atc cct gcc aaa ttt Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe 210 215 220	672
cca agc aag aac ctg aag atg aat tat tgc cac aac cct gac ggg gag Pro Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu 225 230 235 240	720
cca agg ccc tgg tgc ttc aca aca gac ccc acc aaa cgc tgg gaa tac Pro Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr 245 250 255	768
tgt gac atc ccc cgc tgc aca aca ccc ccg ccc cca ccc agc cca acc Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Ser Pro Thr 260 265 270	816
tac caa tgt ctg aaa gga aga ggt gaa aat tac cga ggg acc gtg tct Tyr Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser	864

275	280	285	
gtc acc gtg tct ggg aaa acc tgc cag cgc tgg agt gag caa acc cct Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro			912
290	295	300	
cat agg cac aac agg aca cca gaa aat ttc ccc tgc aaa aat ctg gaa His Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu			960
305	310	315	320
gag aac tac tgc cgg aac cca gat gga gaa act gct ccc tgg tgc tat Glu Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr			1008
325	330	335	
acc act gac agc cag ctg agg tgg gag tac tgt gag att cca tcc tgc Thr Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys			1056
340	345	350	
gag tcc tca gca tca cca gac cag tca gat tcc tca gtt cca cca gag Glu Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu			1104
355	360	365	
gag caa aca cct gtg gtc cag gaa tgc tac cag agc gat ggg cag agc Glu Gln Thr Pro Val Val Gln Glu Cys Tyr Gln Ser Asp Gly Gln Ser			1152
370	375	380	
tat cgg ggt aca tcg tcc act acc atc aca ggg aag aag tgc cag tcc Tyr Arg Gly Thr Ser Ser Thr Thr Ile Thr Gly Lys Lys Cys Gln Ser			1200
385	390	395	400
tgg gca gct atg ttt cca cac agg cat tcg aag acc cca gag aac ttc Trp Ala Ala Met Phe Pro His Arg His Ser Lys Thr Pro Glu Asn Phe			1248
405	410	415	
cca gat gct ggc ttg gag atg aac tac tgc agg aac ccg gat ggt gac Pro Asp Ala Gly Leu Glu Met Asn Tyr Cys Arg Asn Pro Asp Gly Asp			1296
420	425	430	
aag ggc cct tgg tgc tac acc act gac ccg agc gtc agg tgg gaa tac Lys Gly Pro Trp Cys Tyr Thr Asp Pro Ser Val Arg Trp Glu Tyr			1344
435	440	445	
tgc aac ctg aag cgg tgc tca gag aca gga ggg aat tca gac tac aag Cys Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly Asn Ser Asp Tyr Lys			1392
450	455	460	
gac gac gat gac aag taa taa c Asp Asp Asp Asp Lys * *			1414
465			

<210> 12
 <211> 469
 <212> PRT
 <213> Mus musculus

<400> 12
 Met Asp His Lys Glu Val Ile Leu Leu Phe Leu Leu Leu Lys Pro
 1 5 10 15
 Gly Gln Gly Asp Ser Leu Asp Gly Tyr Ile Ser Thr Gln Gly Ala Ser
 20 25 30
 Leu Phe Ser Leu Thr Lys Lys Gln Leu Ala Ala Gly Gly Val Ser Asp
 35 40 45
 Cys Leu Ala Lys Cys Glu Gly Glu Thr Asp Phe Val Cys Arg Ser Phe
 50 55 60
 Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Ser
 65 70 75 80
 Lys Thr Ser Ser Ile Ile Arg Met Arg Asp Val Ile Leu Phe Glu Lys
 85 90 95
 Arg Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg
 100 105 110
 Gly Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly
 115 120 125
 Ala Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn
 130 135 140
 Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln
 145 150 155 160
 Gly Pro Trp Cys Tyr Thr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys
 165 170 175
 Asn Ile Pro Glu Cys Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys
 180 185 190
 Tyr Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala
 195 200 205
 Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe
 210 215 220
 Pro Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu
 225 230 235 240
 Pro Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr
 245 250 255
 Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Ser Pro Thr
 260 265 270
 Tyr Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser
 275 280 285
 Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro
 290 295 300
 His Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu
 305 310 315 320
 Glu Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr
 325 330 335
 Thr Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys
 340 345 350
 Glu Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Val Pro Pro Glu
 355 360 365
 Glu Gln Thr Pro Val Val Gln Glu Cys Tyr Gln Ser Asp Gly Gln Ser
 370 375 380
 Tyr Arg Gly Thr Ser Ser Thr Thr Ile Thr Gly Lys Lys Cys Gln Ser
 385 390 395 400
 Trp Ala Ala Met Phe Pro His Arg His Ser Lys Thr Pro Glu Asn Phe
 405 410 415 420
 Pro Asp Ala Gly Leu Glu Met Asn Tyr Cys Arg Asn Pro Asp Gly Asp
 420 425 430

Lys Gly Pro Trp Cys Tyr Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr
 435 440 445
 Cys Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly Asn Ser Asp Tyr Lys
 450 455 460
 Asp Asp Asp Asp Lys
 465

<210> 13
 <211> 661
 <212> DNA
 <213> Mus musculus

<220>
 <221> CDS
 <222> (1)...(661)

<400> 13

atg	gac	cat	aag	gaa	gta	atc	ctt	ctg	ttt	ctc	ttg	ctt	ctg	aaa	cca	48
Met	Asp	His	Lys	Glu	Val	Ile	Leu	Leu	Phe	Leu	Leu	Leu	Leu	Lys	Pro	
1															15	

gga	caa	ggg	gac	tcg	cta	gat	ctt	gac	tac	aag	gac	gac	gat	gac	aag	96
Gly	Gln	Gly	Asp	Ser	Leu	Asp	Leu	Asp	Tyr	Lys	Asp	Asp	Asp	Asp	Lys	
															20	
															25	
															30	

ctt	gct	cat	act	cat	cag	gac	ttt	cag	cca	gtg	ctc	cac	ctg	gtg	gca	144
Leu	Ala	His	Thr	His	Gln	Asp	Phe	Gln	Pro	Val	Leu	His	Leu	Val	Ala	
															35	
															40	
															45	

ctg	aac	acc	ccc	ctg	tct	gga	ggc	atg	cgt	ggt	atc	cgt	gga	gca	gat	192
Leu	Asn	Thr	Pro	Leu	Ser	Gly	Gly	Met	Arg	Gly	Ile	Arg	Gly	Ala	Asp	
															50	
															55	
															60	

ttc	cag	tgc	ttc	cag	caa	gcc	cga	gcc	gtg	ggg	ctg	tcg	ggc	acc	ttc	240
Phe	Gln	Cys	Phe	Gln	Gln	Ala	Arg	Ala	Val	Gly	Leu	Ser	Gly	Thr	Phe	
															65	
															70	
															75	
															80	

cgg	gct	ttc	ctg	tcc	tct	agg	ctg	cag	gat	ctc	tat	agc	atc	gtg	cgc	288
Arg	Ala	Phe	Leu	Ser	Ser	Arg	Leu	Gln	Asp	Leu	Tyr	Ser	Ile	Val	Arg	
															85	
															90	
															95	

cgt	gct	gac	cgg	ggg	tct	gtg	ccc	atc	gtc	aac	ctg	aag	gac	gag	gtg	336
Arg	Ala	Asp	Arg	Gly	Ser	Val	Pro	Ile	Val	Asn	Leu	Lys	Asp	Glu	Val	
															100	
															105	
															110	

cta	tct	ccc	agc	tgg	gac	tcc	ctg	ttt	tct	ggc	tcc	cag	ggt	caa	gtg	384
Leu	Ser	Pro	Ser	Trp	Asp	Ser	Leu	Phe	Ser	Gly	Ser	Gln	Gly	Gln	Val	
															115	
															120	
															125	

caa	ccc	ggg	gcc	cgc	atc	ttt	tct	ttt	gac	ggc	aga	gat	gtc	ctg	aga	432
Gln	Pro	Gly	Ala	Arg	Ile	Phe	Ser	Phe	Asp	Gly	Arg	Asp	Val	Leu	Arg	
															130	
															135	
															140	

cac	cca	gcc	tgg	ccg	cag	aag	agc	gta	tgg	cac	ggc	tcg	gac	ccc	agt	480
His	Pro	Ala	Trp	Pro	Gln	Lys	Ser	Val	Trp	His	Gly	Ser	Asp	Pro	Ser	

145	150	155	160	
ggg cgg agg ctg atg gag agt tac tgt gag aca tgg cga act gaa act				528
Gly Arg Arg Leu Met Glu Ser Tyr Cys Glu Thr Trp Arg Thr Glu Thr				
165	170	175		
act ggg gct aca ggt cag gcc tcc tcc ctg ctg tca ggc agg ctc ctg				576
Thr Gly Ala Thr Gly Gln Ala Ser Ser Leu Leu Ser Gly Arg Leu Leu				
180	185	190		
gaa cag aaa gct gcg agc tgc cac aac agc tac atc gtc ctg tgc att				624
Glu Gln Lys Ala Ala Ser Cys His Asn Ser Tyr Ile Val Leu Cys Ile				
195	200	205		
gag aat agc ttc atg acc tct ttc tcc aaa taa taa c				661
Glu Asn Ser Phe Met Thr Ser Phe Ser Lys * *				
210	215			
<210> 14				
<211> 218				
<212> PRT				
<213> Mus musculus				
<400> 14				
Met Asp His Lys Glu Val Ile Leu Leu Phe Leu Leu Leu Lys Pro				
1	5	10	15	
Gly Gln Gly Asp Ser Leu Asp Leu Asp Tyr Lys Asp Asp Asp Asp Lys				
20	25	30		
Leu Ala His Thr His Gln Asp Phe Gln Pro Val Leu His Leu Val Ala				
35	40	45		
Leu Asn Thr Pro Leu Ser Gly Gly Met Arg Gly Ile Arg Gly Ala Asp				
50	55	60		
Phe Gln Cys Phe Gln Gln Ala Arg Ala Val Gly Leu Ser Gly Thr Phe				
65	70	75	80	
Arg Ala Phe Leu Ser Ser Arg Leu Gln Asp Leu Tyr Ser Ile Val Arg				
85	90	95		
Arg Ala Asp Arg Gly Ser Val Pro Ile Val Asn Leu Lys Asp Glu Val				
100	105	110		
Leu Ser Pro Ser Trp Asp Ser Leu Phe Ser Gly Ser Gln Gly Gln Val				
115	120	125		
Gln Pro Gly Ala Arg Ile Phe Ser Phe Asp Gly Arg Asp Val Leu Arg				
130	135	140		
His Pro Ala Trp Pro Gln Lys Ser Val Trp His Gly Ser Asp Pro Ser				
145	150	155	160	
Gly Arg Arg Leu Met Glu Ser Tyr Cys Glu Thr Trp Arg Thr Glu Thr				
165	170	175		
Thr Gly Ala Thr Gly Gln Ala Ser Ser Leu Leu Ser Gly Arg Leu Leu				
180	185	190		
Glu Gln Lys Ala Ala Ser Cys His Asn Ser Tyr Ile Val Leu Cys Ile				
195	200	205		
Glu Asn Ser Phe Met Thr Ser Phe Ser Lys				
210	215			
<210> 15				

<211> 1747
 <212> DNA
 <213> Mus musculus

 <220>
 <221> CDS
 <222> (1) ... (1747)

 <400> 15

atg	gac	cat	aag	gaa	gta	atc	ctt	ctg	ttt	ctc	ttg	ctt	ctg	aaa	cca	48
Met	Asp	His	Lys	Glu	Val	Ile	Leu	Leu	Phe	Leu	Leu	Leu	Leu	Lys	Pro	
1															15	
5																
gga	caa	ggg	gac	tcg	ctg	gat	ggc	tac	ata	agc	aca	caa	ggg	gct	tca	96
Gly	Gln	Gly	Asp	Ser	Leu	Asp	Gly	Tyr	Ile	Ser	Thr	Gln	Gly	Ala	Ser	
20															30	
ctg	ttc	agt	ctc	acc	aag	aag	cag	ctc	gca	gca	gga	ggt	gtc	tcg	gac	144
Leu	Phe	Ser	Leu	Thr	Lys	Lys	Gln	Leu	Ala	Ala	Gly	Gly	Val	Ser	Asp	
35															45	
tgt	ttg	gcc	aaa	tgt	gaa	ggg	gaa	aca	gac	ttt	gtc	tgc	agg	tca	ttc	192
Cys	Leu	Ala	Lys	Cys	Glu	Gly	Glu	Thr	Asp	Phe	Val	Cys	Arg	Ser	Phe	
50																
cag	tac	cac	agc	aaa	gag	cag	caa	tgc	gtg	atc	atg	gcg	gag	aac	agc	240
Gln	Tyr	His	Ser	Lys	Glu	Gln	Gln	Cys	Val	Ile	Met	Ala	Glu	Asn	Ser	
65															80	
aag	act	tcc	tcc	atc	atc	cg	atg	aga	gac	gtc	atc	tta	ttc	gaa	aag	288
Lys	Thr	Ser	Ser	Ile	Ile	Arg	Met	Arg	Asp	Val	Ile	Leu	Phe	Glu	Lys	
85															95	
aga	gtg	tat	ctg	tca	gaa	tgt	aag	acc	ggc	atc	ggc	aac	ggc	tac	aga	336
Arg	Val	Tyr	Leu	Ser	Glu	Cys	Lys	Thr	Gly	Ile	Gly	Asn	Gly	Tyr	Arg	
100															110	
gga	acc	atg	tcc	agg	aca	aag	agt	ggt	gtt	gcc	tgt	caa	aag	tgg	gg	384
Gly	Thr	Met	Ser	Arg	Thr	Lys	Ser	Gly	Val	Ala	Cys	Gln	Lys	Trp	Gly	
115															125	
gcc	acg	tcc	ccc	cac	gta	ccc	aac	tac	tct	ccc	agt	aca	cat	ccc	aat	432
Ala	Thr	Phe	Pro	His	Val	Pro	Asn	Tyr	Ser	Pro	Ser	Thr	His	Pro	Asn	
130															140	
gag	gga	cta	gaa	gag	aac	tac	tgt	agg	aac	cca	gac	aat	gat	gaa	caa	480
Glu	Gly	Leu	Glu	Glu	Asn	Tyr	Cys	Arg	Asn	Pro	Asp	Asn	Asp	Glu	Gln	
145															160	
ggg	cct	tgg	tgc	tac	act	aca	gat	ccg	gac	aag	aga	tat	gac	tac	tgc	528
Gly	Pro	Trp	Cys	Tyr	Thr	Thr	Asp	Pro	Asp	Lys	Arg	Tyr	Asp	Tyr	Cys	
165															175	
aac	att	cct	gaa	tgt	gaa	gag	gaa	tgc	atg	tac	tgc	agt	gga	gaa	aag	576
Asn	Ile	Pro	Glu	Cys	Glu	Glu	Cys	Met	Tyr	Cys	Ser	Gly	Glu	Lys		

180	185	190	
tat gag ggc aaa atc tcc aag acc atg tct gga ctt gac tgc cag gcc Tyr Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala 195 200 205			624
tgg gat tct cag agc cca cat gct cat gga tac atc cct gcc aaa ttt Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe 210 215 220			672
cca agc aag aac ctg aag atg aat tat tgc cac aac cct gac ggg gag Pro Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu 225 230 235 240			720
cca agg ccc tgg tgc ttc aca aca gac ccc acc aaa cgc tgg gaa tac Pro Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr 245 250 255			768
tgt gac atc ccc cgc tgc aca aca ccc ccg ccc cca ccc agc cca acc Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Pro Ser Pro Thr 260 265 270			816
tac caa tgt ctg aaa gga aga ggt gaa aat tac cga ggg acc gtg tct Tyr Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser 275 280 285			864
gtc acc gtg tct ggg aaa acc tgt cag cgc tgg agt gag caa acc cct Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro 290 295 300			912
cat agg cac aac agg aca cca gaa aat ttc ccc tgc aaa aat ctg gaa His Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu 305 310 315 320			960
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gat ctt gac tac aag gac gac gat gac aag ctt gct cat act cat cag Asp Leu Asp Tyr Lys Asp Asp Asp Asp Lys Leu Ala His Thr His Gln 385 390 395			1200
gac ttt cag cca gtg ctc cac ctg gtg gca ctg aac acc ccc ctg tct			1248

Asp Phe Gln Pro Val Leu His Leu Val Ala Leu Asn Thr Pro Leu Ser		
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Gly Gly Met Arg Gly Ile Arg Gly Ala Asp Phe Gln Cys Phe Gln Gln		
420	425	430
gcc cga gcc gtg ggg ctg tcg ggc acc ttc cgg gct ttc ctg tcc tct		1344
Ala Arg Ala Val Gly Leu Ser Gly Thr Phe Arg Ala Phe Leu Ser Ser		
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agg ctg cag gat ctc tat agc atc gtg cgc cgt gct gac cgg ggg tct		1392
Arg Leu Gln Asp Leu Tyr Ser Ile Val Arg Arg Ala Asp Arg Gly Ser		
450	455	460
gtg ccc atc gtc aac ctg aag gac gag gtg cta tct ccc agc tgg gac		1440
Val Pro Ile Val Asn Leu Lys Asp Glu Val Leu Ser Pro Ser Trp Asp		
465	470	475
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Ser Leu Phe Ser Gly Ser Gln Gly Gln Val Gln Pro Gly Ala Arg Ile		
485	490	495
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Phe Ser Phe Asp Gly Arg Asp Val Leu Arg His Pro Ala Trp Pro Gln		
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Lys Ser Val Trp His Gly Ser Asp Pro Ser Gly Arg Arg Leu Met Glu		
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agt tac tgt gag aca tgg cga act gaa act act ggg gct aca ggt cag		1632
Ser Tyr Cys Glu Thr Trp Arg Thr Glu Thr Thr Gly Ala Thr Gly Gln		
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Ala Ser Ser Leu Leu Ser Gly Arg Leu Leu Glu Gln Lys Ala Ala Ser		
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Cys His Asn Ser Tyr Ile Val Leu Cys Ile Glu Asn Ser Phe Met Thr		
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Ser Phe Ser Lys * *		
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<212> PRT		
<213> Mus musculus		
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35	40	45													
Cys	Leu	Ala	Lys	Cys	Glu	Gly	Glu	Thr	Asp	Phe	Val	Cys	Arg	Ser	Phe
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Gln	Tyr	His	Ser	Lys	Glu	Gln	Gln	Cys	Val	Ile	Met	Ala	Glu	Asn	Ser
65	70	75	80												
Lys	Thr	Ser	Ser	Ile	Ile	Arg	Met	Arg	Asp	Val	Ile	Leu	Phe	Glu	Lys
85	90	95													
Arg	Val	Tyr	Leu	Ser	Glu	Cys	Lys	Thr	Gly	Ile	Gly	Asn	Gly	Tyr	Arg
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115	120	125													
Ala	Thr	Phe	Pro	His	Val	Pro	Asn	Tyr	Ser	Pro	Ser	Thr	His	Pro	Asn
130	135	140													
Glu	Gly	Leu	Glu	Glu	Asn	Tyr	Cys	Arg	Asn	Pro	Asp	Asn	Asp	Glu	Gln
145	150	155	160												
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165	170	175													
Asn	Ile	Pro	Glu	Cys	Glu	Glu	Glu	Cys	Met	Tyr	Cys	Ser	Gly	Glu	Lys
180	185	190													
Tyr	Glu	Gly	Lys	Ile	Ser	Lys	Thr	Met	Ser	Gly	Leu	Asp	Cys	Gln	Ala
195	200	205													
Trp	Asp	Ser	Gln	Ser	Pro	His	Ala	His	Gly	Tyr	Ile	Pro	Ala	Lys	Phe
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225	230	235	240												
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245	250	255													
Cys	Asp	Ile	Pro	Arg	Cys	Thr	Thr	Pro	Pro	Pro	Pro	Pro	Ser	Pro	Thr
260	265	270													
Tyr	Gln	Cys	Leu	Lys	Gly	Arg	Gly	Glu	Asn	Tyr	Arg	Gly	Thr	Val	Ser
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Val	Thr	Val	Ser	Gly	Lys	Thr	Cys	Gln	Arg	Trp	Ser	Glu	Gln	Thr	Pro
290	295	300													
His	Arg	His	Asn	Arg	Thr	Pro	Glu	Asn	Phe	Pro	Cys	Lys	Asn	Leu	Glu
305	310	315	320												
Glu	Asn	Tyr	Cys	Arg	Asn	Pro	Asp	Gly	Glu	Thr	Ala	Pro	Trp	Cys	Tyr
325	330	335													
Thr	Thr	Asp	Ser	Gln	Leu	Arg	Trp	Glu	Tyr	Cys	Glu	Ile	Pro	Ser	Cys
340	345	350													
Glu	Ser	Ser	Ala	Ser	Pro	Asp	Gln	Ser	Asp	Ser	Ser	Val	Pro	Pro	Glu
355	360	365													
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Asp	Leu	Asp	Tyr	Lys	Asp	Asp	Asp	Asp	Lys	Leu	Ala	His	Thr	His	Gln
385	390	395	400												
Asp	Phe	Gln	Pro	Val	Leu	His	Leu	Val	Ala	Leu	Asn	Thr	Pro	Leu	Ser
405	410	415													
Gly	Gly	Met	Arg	Gly	Ile	Arg	Gly	Ala	Asp	Phe	Gln	Cys	Phe	Gln	Gln
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<211> 549
<212> DNA
<213> *Homo sapiens*

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gaggctccct cggccacggg ccaggctcc tcgctgtgg ggggcaggt cctggggcag 480
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<211> 183
<212> PRT
<213> *Homo sapiens*

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				20				25				30			
Cys	Phe	Gln	Gln	Ala	Arg	Ala	Val	Gly	Leu	Ala	Gly	Thr	Phe	Arg	Ala
	35				40							45			
Phe	Leu	Ser	Ser	Arg	Leu	Gln	Asp	Leu	Tyr	Ser	Ile	Val	Arg	Arg	Ala
	50					55						60			
Asp	Arg	Ala	Ala	Val	Pro	Ile	Val	Asn	Leu	Lys	Asp	Glu	Leu	Leu	Phe
	65					70				75				80	
Pro	Ser	Trp	Glu	Ala	Leu	Phe	Ser	Gly	Ser	Glu	Gly	Pro	Leu	Lys	Pro
					85				90				95		
Gly	Ala	Arg	Ile	Phe	Ser	Phe	Asp	Gly	Lys	Asp	Val	Leu	Arg	His	Pro

100	105	110
Thr Trp Pro Gln Lys Ser Val Trp His Gly Ser Asp Pro Asn Gly Arg		
115	120	125
Arg Leu Thr Glu Ser Tyr Cys Glu Thr Trp Arg Thr Glu Ala Pro Ser		
130	135	140
Ala Thr Gly Gln Ala Ser Ser Leu Leu Gly Gly Arg Leu Leu Gly Gln		
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<210> 19
 <211> 5408
 <212> DNA
 <213> Homo sapiens

<400> 19

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 <212> PRT
 <213> Homo sapiens

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 20 25 30
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 35 40 45
 Gly Asp Pro Pro Pro Gln Gln Val Thr Gln Thr Asp Asp Pro Asp Val
 50 55 60
 Gly Leu Ala Tyr Val Phe Gly Pro Asp Ala Asn Ser Gly Gln Val Ala
 65 70 75 80
 Arg Tyr His Phe Pro Ser Leu Phe Phe Arg Asp Phe Ser Leu Leu Phe
 85 90 95
 His Ile Arg Pro Ala Thr Glu Gly Pro Gly Val Leu Phe Ala Ile Thr
 100 105 110
 Asp Ser Ala Gln Ala Met Val Leu Leu Gly Val Lys Leu Ser Gly Val
 115 120 125
 Gln Asp Gly His Gln Asp Ile Ser Leu Leu Tyr Thr Glu Pro Gly Ala
 130 135 140
 Gly Gln Thr His Thr Ala Ala Ser Phe Arg Leu Pro Ala Phe Val Gly
 145 150 155 160
 Gln Trp Thr His Leu Ala Leu Ser Val Ala Gly Gly Phe Val Ala Leu
 165 170 175
 Tyr Val Asp Cys Glu Glu Phe Gln Arg Met Pro Leu Ala Arg Ser Ser
 180 185 190
 Arg Gly Leu Glu Leu Glu Pro Gly Ala Gly Leu Phe Val Ala Gln Ala
 195 200 205
 Gly Gly Ala Asp Pro Asp Lys Phe Gln Gly Val Ile Ala Glu Leu Lys
 210 215 220
 Val Arg Arg Asp Pro Gln Val Ser Pro Met His Cys Leu Asp Glu Glu
 225 230 235 240
 Gly Asp Asp Ser Asp Gly Ala Phe Gly Asp Ser Gly Ser Gly Leu Gly
 245 250 255
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 260 265 270
 Arg Leu Pro Ala Pro Pro Val Thr Thr Pro Pro Leu Ala Gly Gly
 275 280 285
 Ser Ser Thr Glu Asp Ser Arg Ser Glu Glu Val Glu Glu Gln Thr Thr
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 Val Ala Ser Leu Gly Ala Gln Thr Leu Pro Gly Ser Asp Ser Val Ser
 305 310 315 320
 Thr Trp Asp Gly Ser Val Arg Thr Pro Gly Gly Arg Val Lys Glu Gly
 325 330 335
 Gly Leu Lys Gly Gln Lys Gly Glu Pro Gly Val Pro Gly Pro Pro Gly
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 Arg Ala Gly Pro Pro Gly Ser Pro Cys Leu Pro Gly Pro Pro Gly Leu
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 Pro Cys Pro Val Ser Pro Leu Gly Pro Ala Gly Pro Ala Leu Gln Thr
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Val Pro Gly Pro Gln Gly Pro Pro Gly Pro Pro Gly Arg Asp Gly Thr
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 Pro Gly Arg Asp Gly Glu Pro Gly Asp Pro Gly Glu Asp Gly Lys Pro
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 Gly Asp Thr Gly Pro Gln Gly Phe Pro Gly Thr Pro Gly Asp Val Gly
 420 425 430
 Pro Lys Gly Asp Lys Gly Asp Pro Gly Val Gly Glu Arg Gly Pro Pro
 435 440 445
 Gly Pro Gln Gly Pro Pro Gly Pro Pro Gly Pro Ser Phe Arg His Asp
 450 455 460
 Lys Leu Thr Phe Ile Asp Met Glu Gly Ser Gly Phe Gly Gly Asp Leu
 465 470 475 480
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 485 490 495
 Gly Val Pro Gly Leu Pro Gly Glu Pro Gly Arg Phe Gly Val Asn Ser
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 Ser Asp Val Pro Gly Pro Ala Gly Leu Pro Gly Val Pro Gly Arg Glu
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 Gly Pro Pro Gly Phe Pro Gly Leu Pro Gly Pro Pro Gly Pro Pro Gly
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 Arg Glu Gly Pro Pro Gly Arg Thr Gly Gln Lys Gly Ser Leu Gly Glu
 545 550 555 560
 Ala Gly Ala Pro Gly His Lys Gly Ser Lys Gly Ala Pro Gly Pro Ala
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 Gly Ala Arg Gly Glu Ser Gly Leu Ala Gly Ala Pro Gly Pro Ala Gly
 580 585 590
 Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Gly Leu Pro
 595 600 605
 Ala Gly Phe Asp Asp Met Glu Gly Ser Gly Gly Pro Phe Trp Ser Thr
 610 615 620
 Ala Arg Ser Ala Asp Gly Pro Gln Gly Pro Pro Gly Leu Pro Gly Leu
 625 630 635 640
 Lys Gly Asp Pro Gly Val Pro Gly Leu Pro Gly Ala Lys Gly Glu Val
 645 650 655
 Gly Ala Asp Gly Ile Pro Gly Phe Pro Gly Leu Pro Gly Arg Glu Gly
 660 665 670
 Ile Ala Gly Pro Gln Gly Pro Lys Gly Asp Arg Gly Ser Arg Gly Glu
 675 680 685
 Lys Gly Asp Pro Gly Lys Asp Gly Val Gly Gln Pro Gly Leu Pro Gly
 690 695 700
 Pro Pro Gly Pro Pro Gly Pro Val Val Tyr Val Ser Glu Gln Asp Gly
 705 710 715 720
 Ser Val Leu Ser Val Pro Gly Pro Glu Gly Arg Pro Gly Phe Ala Gly
 725 730 735
 Phe Pro Gly Pro Ala Gly Pro Lys Gly Asn Leu Gly Ser Lys Gly Glu
 740 745 750
 Arg Gly Ser Pro Gly Pro Lys Gly Glu Lys Gly Glu Pro Gly Ser Ile
 755 760 765
 Phe Ser Pro Asp Gly Gly Ala Leu Gly Pro Ala Gln Lys Gly Ala Lys
 770 775 780
 Gly Glu Pro Gly Phe Arg Gly Pro Pro Gly Pro Tyr Gly Arg Pro Gly
 785 790 795 800
 Tyr Lys Gly Glu Ile Gly Phe Pro Gly Arg Pro Gly Arg Pro Gly Met
 805 810 815
 Asn Gly Leu Lys Gly Glu Lys Gly Glu Pro Gly Asp Ala Ser Leu Gly

820	825	830														
Phe	Gly	Met	Arg	Gly	Met	Pro	Gly	Pro	Pro	Gly	Pro	Pro	Phe	Gly	Pro	Pro
835	840	845														
Gly	Pro	Pro	Gly	Thr	Pro	Val	Tyr	Asp	Ser	Asn	Val	Phe	Ala	Glu	Ser	
850	855	860														
Ser	Arg	Pro	Gly	Pro	Pro	Gly	Leu	Pro	Gly	Asn	Gln	Gly	Pro	Pro	Gly	
865	870	875	880													
Pro	Lys	Gly	Ala	Lys	Gly	Glu	Val	Gly	Pro	Pro	Gly	Pro	Gly	Gln		
885	890	895														
Phe	Pro	Phe	Asp	Phe	Leu	Gln	Leu	Glu	Ala	Glu	Met	Lys	Gly	Glu	Lys	
900	905	910														
Gly	Asp	Arg	Gly	Asp	Ala	Gly	Gln	Lys	Gly	Glu	Arg	Gly	Glu	Pro	Gly	
915	920	925														
Gly	Gly	Gly	Phe	Phe	Gly	Ser	Ser	Leu	Pro	Gly	Pro	Pro	Gly	Pro	Pro	
930	935	940														
Gly	Pro	Arg	Gly	Tyr	Pro	Gly	Ile	Pro	Gly	Pro	Lys	Gly	Ser	Ile		
945	950	955	960													
Arg	Gly	Gln	Pro	Gly	Pro	Pro	Gly	Pro	Gln	Gly	Pro	Pro	Gly	Ile	Gly	
965	970	975														
Tyr	Glu	Gly	Arg	Gln	Gly	Pro	Pro	Gly	Pro	Pro	Gly	Pro	Pro	Gly	Pro	
980	985	990														
Pro	Ser	Phe	Pro	Gly	Pro	His	Arg	Gln	Thr	Ile	Ser	Val	Pro	Gly	Pro	
995	1000	1005														
Pro	Gly	Pro	Pro	Gly	Pro	Pro	Gly	Pro	Pro	Gly	Thr	Met	Gly	Ala	Ser	
1010	1015	1020														
Ser	Gly	Val	Arg	Leu	Trp	Ala	Thr	Arg	Gln	Ala	Met	Leu	Gly	Gln	Val	
1025	1030	1035	104													
His	Glu	Val	Pro	Glü	Gly	Trp	Leu	Ile	Phe	Val	Ala	Glu	Gln	Glu	Glu	
1045	1050	1055														
Leu	Tyr	Val	Arg	Val	Gln	Asn	Gly	Phe	Arg	Lys	Val	Gln	Leu	Glu	Ala	
1060	1065	1070														
Arg	Thr	Pro	Leu	Pro	Arg	Gly	Thr	Asp	Asn	Glu	Val	Ala	Ala	Leu	Gln	
1075	1080	1085														
Pro	Pro	Val	Val	Gln	Leu	His	Asp	Ser	Asn	Pro	Tyr	Pro	Arg	Arg	Glu	
1090	1095	1100														
His	Pro	His	Pro	Thr	Ala	Arg	Pro	Trp	Arg	Ala	Asp	Asp	Ile	Leu	Ala	
1105	1110	1115	112													
Ser	Pro	Pro	Arg	Leu	Pro	Glu	Pro	Gln	Pro	Tyr	Pro	Gly	Ala	Pro	His	
1125	1130	1135														
His	Ser	Ser	Tyr	Val	His	Leu	Arg	Pro	Ala	Arg	Pro	Thr	Ser	Pro	Pro	
1140	1145	1150														
Ala	His	Ser	His	Arg	Asp	Phe	Gln	Pro	Val	Leu	His	Leu	Val	Ala	Leu	
1155	1160	1165														
Asn	Ser	Pro	Leu	Ser	Gly	Gly	Met	Arg	Gly	Ile	Arg	Gly	Ala	Asp	Phe	
1170	1175	1180														
Gln	Cys	Phe	Gln	Gln	Ala	Arg	Ala	Val	Gly	Leu	Ala	Gly	Thr	Phe	Arg	
1185	1190	1195	120													
Ala	Phe	Leu	Ser	Ser	Arg	Leu	Gln	Asp	Leu	Tyr	Ser	Ile	Val	Arg	Arg	
1205	1210	1215														
Ala	Asp	Arg	Ala	Ala	Val	Pro	Ile	Val	Asn	Leu	Lys	Asp	Glu	Leu	Leu	
1220	1225	1230														
Phe	Pro	Ser	Trp	Glu	Ala	Leu	Phe	Ser	Gly	Ser	Glu	Gly	Pro	Leu	Lys	
1235	1240	1245														
Pro	Gly	Ala	Arg	Ile	Phe	Ser	Phe	Asp	Gly	Lys	Asp	Val	Leu	Arg	His	
1250	1255	1260														

Pro Thr Trp Pro Gln Lys Ser Val Trp His Gly Ser Asp Pro Asn Gly
1265 1270 1275 128
Arg Arg Leu Thr Glu Ser Tyr Cys Glu Thr Trp Arg Thr Glu Ala Pro
1285 1290 1295
Ser Ala Thr Gly Gln Ala Ser Ser Leu Leu Gly Gly Arg Leu Leu Gly
1300 1305 1310
Gln Ser Ala Ala Ser Cys His His Ala Tyr Ile Val Leu Cys Ile Glu
1315 1320 1325
Asn Ser Phe Met Thr Ala Ser Lys
1330 1335

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/24950

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A01N 63/00, 43/04; C12N 15/00; C07H 21/02
 US CL : 424/93.1; 435/320.1; 514/44; 536/23.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/93.1; 435/320.1; 514/44; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	US 5,792,845 A (O'REILLY et al.) 11 August 1998 (11.08.98), col. 4, lines 32-68, col. 5, lines 1-2, 51-68, col. 6, lines 1-8.	1-30, 33
Y	WO 97/23500 A1 (THE CHILDREN'S MEDICAL CENTER CORPORATION) 03 July 1997 (03.07.97), page 41, lines 3-33, page 42, lines 1-27.	4
X,P ----- Y,P	WO 98/49321 A2 (RHONE-POULENC RORER) 05 November 1998 (05.11.98), page 44, 6-11, 25-33, page 45, lines 12-13, 29-35.	1, 5, 18, 20, 31 ----- 2-4, 6-17, 19, 21-30, 32, 33

Further documents are listed in the continuation of Box C. See patent family annex.

Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

04 FEBRUARY 1999

Date of mailing of the international search report

08 MAR 1999

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/24950

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97/15666 A (THE CHILDREN'S MEDICAL CENTER CORPORATION) 01 May 1997 (01.05.97), page 20, lines 16-35, page 21, page 22, lines 1-16. page 59, lines 5-35, page 60, page 61, 1-6.	1-30, 33
Y	TANAKA, T. et al. Retroviral and adenoviral mediated transduction of angiostatin cDNA inhibits angiogenesis and tumor growth. Proceedings of the American Association for Cancer Research. March 1997 (03.97). Vol 38. page 264.	1-33
Y	WO 96/35774 A2 (THE CHILDREN'S MEDICAL CENTER CORPORATION) 14 November 1996 (14.11.96), page lines 33-36, pages 22-25, page 26, lines 1-33. pages 144-148.	1-30, 33
Y	WO 97/41824 A2(ABBOTT LABORATORIES) 13 November 1997 (13.11.97), page 5, lines 13-38, page 6, 1-18, page 60, lines 15-38, pages 61-62, page 63, lines 1-33.	1-30, 33
Y	WO 95/29242 A1 (THE CHILDREN'S MEDICAL CENTER CORPORATION) 02 November 1995 (02.11.95), page 21, lines 19-35, pages 22-27, page 28, lines 1-4. page 87, lines 4-35, page 88, page 89, lines 1-14.	1-30, 33
Y	O'REILLY, et al. Angiostatin induces and sustains dormancy of human primary tumors in mice. Nature Medicine, June 1996 (06.96), Vol. 2, No. 6, pages 689-692, especially pages 689-690.	1-30, 33
Y	O'REILLY, et al. Endostatin: An Endogenous Inhibitor of Angiogenesis and Tumor Growth. Cell, 24 January 1997 (24.01.97), Vol. 88, pages 277-285, especially pages 279-280, 282.	1-30, 33

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/24950

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN, WPIDS, MEDLINE, CAPLUS, BIOSIS, EMBASE
search terms: angiostatin, plasminogen, endostatin, collagen(w) XVIII, inhibit?(5a)tumor(5a)growth, tumor(5a)regress?,
diabet?(p)retinopathy, plasmid, viral(5a) vector.

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